COMPARISON OF SALBUTAMOL ADMINISTRATION BY METERED- DOSE INHALER AND SPACER WITH NEBULISER IN ADULTS WITH ACUTE ASTHMA

DISSERTATION SUBMITTED FOR

DOCTOR OF MEDICINE

BRANCH - I (GENERAL MEDICINE)

MARCH 2013

THE TAMILNADU

DR.M.G.R.MEDICAL UNIVERSITY

CHENNAI

BONAFIDE CERTIFICATE

This is to certify that the dissertation entitled "**COMPARISON OF SALBUTAMOL ADMINISTRATION BY METERED- DOSE INHALER AND SPACER WITH NEBULISER IN ADULTS WITH ACUTE ASTHMA** "submitted by **Dr. T.PREETHI SHAHILA** to the Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of M.D Degree Branch–I (General Medicine) is a bonafide research work were carried out by her under my direct supervision & guidance.

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DECLARATION

I, **Dr.T. PREETHI SHAHILA** declare that, I carried out this work on, "**COMPARISON OF SALBUTAMOL ADMINISTRATION BY METERED- DOSE INHALER AND SPACER WITH NEBULISER IN ADULTS WITH ACUTE ASTHMA"** at the Department of Medicine, Govt. Rajaji Hospital during the period of May 2012 to October 2012. I also declare that this bonafide work or a part of this work was not submitted by me or any others for any award, degree, diploma to any other University, Board either in India or abroad.

This is submitted to The Tamilnadu Dr. M. G. R. Medical University, Chennai in partial fulfillment of the rules and regulations for the M.D degree examination in General Medicine.

Place : Madurai **Dr.T. PREETHI SHAHILA**

Date :

ACKNOWLEDGEMENT

At the outset, I wish to thank our Dean ***Dr N.Mohan M.S.,F.I.C.S,*** for permitting me to use the facilities of Madurai Medical College and Government Rajaji Hospital to conduct this study.

My beloved unit chief, Professor and Head of the department of Medicine, **Prof.*Dr.Moses.K.Daniel M.D*.** has always guided me, by example and valuable words of advice and has given me his moral support and encouragement throughout the conduct of the study and also during my postgraduate course. I will be ever grateful to him.

I am extremely grateful to the Professor and Head of the department of pulmonology, **Prof.*Dr.C.Ramesh M.D(chest);D.T.C.D,*** without whose constant support, guidance, cooperation and encouragement this dissertation would not have been possible.

I offer my heartfelt thanks to the Registrar **Dr.Vivekanandan M.D;D.T.C.D**; and to my Assistant Professors ***Dr Sakthimohan.S M.D., Dr Manimegalai M.D., Dr Arul Rajamurugan M.D.D.M.,*** for their constant encouragement, timely help and critical suggestions

throughout the study and also for making my stay in the unit both informative and pleasurable.

I would also like to thank my previous Asst. Professors **Dr. K. Senthil, M.D., Dr. David Pradeepkumar, M.D., Dr. Ganesh Babu, M.D., Dr. Peer Mohamed, M.D., Dr. V.N. Alagu Venkatesan, M.D.,** for their enduring support and encouragement.

I owe my sincere thanks to my colleagues and family who have stood by me during my times of need. Their help and support have been invaluable to this study.

My patients, who form the most integral part of this work, were always kind and cooperative. I pray God give them courage and strength to endure their illness and hope all of them have a good quality of life.

CONTENTS

INTRODUCTION

In the modern era, Bronchial asthma is a disease that is becoming a major health issue in many developing countries. Increased urbanisation may have modified the traditionally low incidence of bronchial asthma in the third world[1]. Depressed socioeconomic conditions may supersede exposure to traffic-related pollution as a factor associated with asthma hospitalization. Although the incidence of new cases of asthma has decreased in recent years, the prevalence of asthma morbidity continues to be a significant clinical and public health issue. The measures of morbidity include the need for urgent medical care and high-dose asthma medications due to uncontrolled asthma symptoms. The word asthma means “panting” or “breathing hard”, it is derived from greek word “aazein”. Asthma is more a clinical diagnosis than a laboratory diagnosis.

Bronchial asthma and the resulting spasm was first described by Greek physician Hippocrates in 460-357 BC. That obstruction to bronchial airways lead to symptoms of asthma was put forth by Greco-Roman physician Galen in 130-201 BC. The occurrence of symptoms does not simply mean constriction of airways, it indicates an underlying inflammatory process which occurs as a result of hyperresponsiveness of airways triggered by an allergen. This was discovered by asthma researchers in 1960[3].

In 2004, Masoli et al and the global initiative for asthma(GINA) with combined data from the phase 1 International study of Asthma and Allergies (ISACC) study conducted in 1992-1996 and the European Community Respiratory Health Survey (ECRHS) in 1994-1998 generated the global estimate of asthma burden, which suggested that the prevalence of asthma symptoms has world wide variations[2]. This report estimated that at present three hundred million people were affected by asthma world wide and by 2025 it would be around four hundred million with increasing urbanisation.

Asthma accounts for around one percent of all Daily Adjusted Life Years lost in the world wide population, which comes to about 15 million per year. It reflects both the high prevalence and severity of asthma[6](GINA2007,Mitchell 1987).The economic loss associated with asthma exceeds those of tuberculosis and HIV/AIDS combined. Improper asthma control is an important factor increasing the cost of subsequent treatment (Van Ganse et al. 2002). Asthma is associated with huge expenditures in health care services which includes hospitalization and medications, loss of work in the form of missed days of work/school that occurs during the period of exacerbations and decline in future earnings. Both these direct and indirect costs are associated with morbidity and mortality.

Until the late 1800s, smoke was used as an agent to deliver medication into lungs. In late 1800s, atropine was used to treat asthma. It was derived from nightshade plant and cigarette was used to deliver the atropine . The secret ingredients of the popular 19th century asthma cures were usually alcohol, cocaine or morphine. The first effective bronchodilator adrenaline was discovered by Jokici Takamine in 1901. In 1960, anti-inflammatory medication and selective short acting beta2-agonists were born.

Initially pressurised MDI was utilised for delivering non-selective beta-agonists adrenaline and isoprenaline. However, the significant number of asthma deaths that occurred in the 1960s led to these drugs being superseded by salbutamol, selective short-acting beta-agonist and beclomethasone, the first inhaled corticosteroid (ICS).

Now a days salbutamol administration with metered- dose inhaler and spacer play a unique role in treatment of acute severe asthma. This study is an attempt to analyse the efficacy of salbutamol administration by Metered Dose Inhaler-spacer compared to a nebuliser in adults with acute asthma.

REVIEW OF LITERATURE

DEFINITION

According to American Thoracic society (1987) Asthma is a clinical syndrome characterized by hyperresponsiveness of tracheobronchial tree to a variety of stimuli. The primary physiological manifestation of this is airway obstruction. The major symptoms of asthma are dry cough, paroxysms of dyspnoea and wheezing which may vary from mild to severe and unremitting asthma (status asthmaticus). This can take the form of spontaneous variation in the severity of obstruction, substantial improvement in the severity of obstruction following bronchodilator or corticosteroid administration or increased obstruction caused by drugs or other stimuli like exercise and challenge test.

EPIDEMIOLOGY[5]

Today in India, Bronchial asthma constitutes 0.5% of National burden of Disease. The total estimated prevalence of asthma in India is 3% (30 million patients) and a median prevalence of 2.4% over the age of 15 (Aggarwal et al 2006). According to National Family Health Survey(NFHS)-3 prevalence of asthma is higher in rural than urban areas. In India, North East regions have the highest prevalence of asthma. In Tamil nadu the prevalence of asthma was 0.9% during 2005-2006.In childhood

asthma incidence is higher in boys than girls, but reverses in the age group of 15-50years and reverses again in the older age group where incidence among men increases once more. Prevalence of asthma among adults in India is similar in men and women. It increases steadily as age advances.

Anatomy of the Lower airways-

They extend from just below the vocal cords of the larynx to the respiratory bronchioles. The lower airways are branching, hollow passageways that conduct air to and from the alveoli. They can alter their diameter which allows them to regulate the speed at which air flows through them. In addition, the larger passages in the lower airways have cartilage rings and plates in their walls giving them some rigidity and preventing collapse .It consists of trachea, bronchi, respiratory bronchioles and alveolar ducts. Cartilaginous airways (trachea and bronchi) serve only to conduct air between external environment and the sites of gas exchange. Non-cartilaginous airways (bronchioles) serve both as conductors of inspired air and sites of gas exchange. Terminal bronchioles are the smallest one and do not take part in gaseous exchange.

The micro structure of the lower airways is as follows:

- Mucosal layer is composed of pseudo stratified ciliated columnar epithelium and contains mucus secreting globlet glands.

- Submucosal layer contains seromucous glands which contributes to the mucous layer of respiratory epithelium.
- Connective tissue in the submucosa consists of elastin bands connected to the elastin networks of inter alveolar septa which is responsible for elastic recoil of the lung and the muscle cells responsible for bronchoconstriction and relaxation.
- Trachea and extra pulmonary bronchi has fibrocartilaginous or fibroelastic tissue forming the framework of connective tissue.

Vascular supply

The bronchi and bronchioles are supplied by the bronchial arteries which are derived from thoracic aorta. Bronchial artery branches supply the submucosa of airways from the capillary plexuses of the muscle layer, by piercing it. Venules originating from these capillaries form venous plexuses by piercing back the muscle layer. Both arteries and venules form plexuses around the muscle layer. On constriction of bronchioles, arterial supply is maintained at systemic pressure but there is obstruction to the venous flow which leads to oedema formation in the bronchial mucosa during an attack of asthma. Pulmonary arteries supply the gas exchanging part of the lung.

Neural supply

Both sensory and autonomic nerves contribute to sympathetic innervation. Sensory nerves act as afferents which begin as free nerve endings and also contain specific bronchial cells (DCGC) which act as neuroepithelial bodies. Autonomic nerves act as efferents which cause broncho constriction, mucus secretion and vasodilation of bronchioles. Parasymphathetic innervation is by vagus.

Types of asthma

1. Extrinsic/Allergic Asthma - This is the most common type and usually begins in childhood(90%).It is due to immunologic response to allergens (aeroallergen, pollens, dust mites, mold, animal dander, ingested foods, beverages or drugs).Type 1 Ig E mediated hypersensitivity reaction occurs in this type. It is characterized by positive family history and attacks preceeded by allergic rhinitis, utricaria or eczema.

2. Intrinsic /non-atopic (Idiopathic asthma) This is the disease of adults (10%) and has a worse prognosis. It is due to endogenous factors like viral infection, chemical irritants, drugs(aspirin) and occupational factors. Atopy test is negative and there is no increase in the concentration of Immunoglobulin E.

3. Nocturnal asthma

This condition usually occurs in early morning hours. It may also occur at night time.

4. Occupational asthma

This is mainly due to pollutants in the environment where the person works and requires prolonged period of exposure. The agents responsible are usually chemical fumes, wood dust and other irritants.

5. Seasonal asthma

This type of asthma is aggravated in certain climates like spring than winter. Pollens which are released from the grass and flowers also contribute to this type of asthma.

6. Bronchial asthma

This is a disease of the lungs in which the airways are stimulated by irritants. These irritants cause inflammation and mucus secretion which cause difficulty in gas exchange and leads to clinical symptoms like shortness of breath, dry cough and tightness of chest.

7. Coughing Variant

Dry cough usually lasts for six to eight weeks in this variant. The airways undergo contracting spasms on exposure to the allergens and environmental irritants. It is common in children.

ETIOLOGY

The etiology of asthma is complex and multifactorial. It is a heterogeneous disease with interplay between genetic and environmental factors. Twin studies(1971)and family history studies(1916 and 1924) done in 16 year old Finnish twins[4] and their parents have reported evidence of genetic connection between serum Ig E concentrations and increased respiratory sensitivity to acetyl choline and exercise challenge test.Monozygotic twins have increased risk than dizygotic twins. Sixty percent risk of atopy is there when both parents are affected. Multiple interactions between genes play an important role. The risk of developing asthma is greatest when both genetic and environmental factors are there.

Genetic Factors- Polymorphism within IL-4(Ch.5q 31-33) ,IL-4R α (ch 16) and IL-13(ch-16) are associated with allergic sensitisation.Polymorphism in TNF is responsible for inflammation rather than allergic response. FcϵRI,IL-4,IL-13 and down regulation of β2Adrenergic receptor gene polymorphisms (Arg16-Gly andGln27-Glu) are responsible for asthma severity. After exposure to the agonist there is substitution of glycine for arginine at codon 16 resulting in increased down-regulation of β_2-Adrnergic receptor . In contrast, a substitution of glutamic acid for glutamine at codon 27 attenuated down- regulation of β_2-Adrenegic receptor. The polymorphism at codon 16 is associated with asthma severity, nocturnal

asthma, and airway hyperresponsiveness. It is not associated with fatal or near fatal asthma.

Recent studies have shown that polymorphisms of ADAM-33 gene *leads to* increased inflammation by causing fibroblast and smooth muscle cell proliferation. This gene belongs to metalloproteinases family and is expressed by lung fibroblasts and bronchial smooth muscle cells. It is also associated with decline in lung function. Further studies are needed to determine the exact function of these genes ,gene-gene interactions and gene-environmental interaction which are undoubtedly complex and remains elusive for now[7].

Environmental factors

In developing countries, the prevalence of asthma is increasing over the last few years indicating the importance of interaction between environmental and genetic factors. The environmental factors like

1. Out door pollutants(ozone, nitrogen dioxide and particles)
2. Indoor pollutants(volatile organic compounds)
3. Diet rich in sodium , poly unsaturated fatty acids like linoleic acid and arachidonic acid or low in antioxidants such as vitamins (A and C), magnesium, selenium, and essential fatty acids in marine and plant oils.

4. Viral respiratory infections

5. Direct enzymatic effect of pollen allergens.

Triggers of asthma

Any condition that causes lower airway inflammation is called a trigger. Thus the inflammed airways contribute to the symptoms of asthma.

Allergic triggers are also known as inflammatory triggers because it causes inflammation of the lungs or spasm of the airway musculature. They include dustmites, animals, cockroaches, moulds, pollens, viral infections and certain air pollutants.

Symptom /non-allergic triggers do not cause inflammation but can stimulate irritant airways especially if they are already inflamed. Symptom triggers include: smoke, exercise, cold air, chemical fumes and strong-smelling substances like perfumes, food additives like sulphites, air pollutants and intense emotions.

Histamine and other mediators which are released from mast cells play a major event in early phases of asthma. In early and late phases of asthma, macrophages and granulocytes also help in releasing the mediators. Stretch and irritant receptors act as cholinergic motor nerves in the airways supplying mucosal glands and bronchial muscles. On triggering attack this

causes smooth muscle contraction of the airways contributing to bronchial asthma. This contraction is not uniform in all the airways.

PATHOGENESIS[8]

The triad of mechanism is as follows

- AIRWAY INFLAMMATION
- AIRWAY HYPERRESPONSIVENESS
- AIR FLOW OBSTRUCTION

Inflammatory macrophages, mast cells and dendritic cells residing in the airway epithelium have a unique role in initiating inflammatory and immune response. Granulocytes and lymphocytes are immune blood-borne cells that get recruited to the inflamed asthmatic airways and play an additional role in the chronic inflammatory process including air way hyperresponsiveness.

Resident cells have low affinity receptors for IgE. During inflammatory response they secrete cytokines which act on the endothelial cells in the microvasculature to cause increased expression of selectin and integrin family groups, required for the entrapment and removal of leucocytes. After the removal of granulocytes, monocytes transform into inflammatory macrophages in the tissue. These inflammatory macrophages secrete chemokines and cytokines which orchestrate the inflammatory

response. They also secrete enzymes and reactive oxygen species and the products of lipoxygenase and cyclooxygenase pathways. Both macrophages and dendritic cells (Antigen presenting cells) are able to cause activation of T-lymphocytes. The myeloid Antigen presenting cells are likely to play a proinflammatory role by expressing the antigen on the surface of T lymphocytes. On first allergen exposure it causes initial sensitisation and on repeated exposures it enhances the inflammation. The incremental and decremental response of inflammation depends on the exposure by the macrophages. The macrophages in the airspaces normally have anti inflammatory effect on lymphocytes but this may be depressed in asthma after exposure to an allergen .Thus macrophages have anti inflammatory response by preventing allergic inflammation.

Mast cells being the source of histamine are found only in asthmatic airways. On allergen exposure they get activated and release preformed mediators apart from histamine like Prostagladin D2,Leukotreine $C_{4,}$ Tumour Necrosis Factor-α ,Vascular Endothelial Growth Factor which also contribute to the inflammatory cascade.

Circulating granulocytes

Basophils secrete histamine due to the triggering effect of high affinity immunoglobulin E receptors on their surface. They are also stimulated by cytokines and eosinophilic and neutrophilic chemokines.

Eosinophils are responsible for the development of hyper responsiveness of airways through the release of proteins, derived from secondary granules. The accumulation of eosinophils in the sensitised tissues is by means of eosinophilic chemokines and cytokine signals like Interleukin-5, eotaxin, Granulocyte Monocyte-Colony Stimulating Factor and RANTES. It differentiates asthma from other inflammatory conditions. Asthmatic individuals have high levels of circulating eosinophils and Charcot Leyden crystals in sputum, derived from the primary granules.

Neutrophils are the resident cells in lung parenchyma. In established asthma ,eosinophils are the predominant cells rather than the neutrophils, but in acute exacerbation neutrophil is the dominant granulocyte. In exacerbations of asthma neutrophil migration may precede eosinophil migration mediated by Interleukin-8. These neutrophils are responsible for mucus secretion and increased vascular permeability during exacerbations.

Lymphocytes- In normal airways Th_1 cells predominate. In asthmatic airways T cell acts as a Th_2 helper cell which secretes Interleukin-4 for IgE production from Immunoglobin G,Interleukin13 for hyperresponsiveness of airways and secretion of mucus and Interleukin-5 for eosinophil recruitment, activation and longevity. Recently it has been found that regulatory T cells have an immunosuppressive effect on T helper cells.

Antigen presenting cells are easily recognised by T helper cells which respond to them.

A complex network of mediators resembling a spider's web is responsible for the unique inflammatory and immunologic response in asthma. Mediators like histamine, prostaglandins and leukotrienes have a pathogenic role in asthma. Kinins are bronchoconstrictors and also vasodilators. They also stimulate sensory nerve endings in the airways, cause exudation of plasma from the microvessels and secretion of mucus in the airways.

Lipid mediators- Cyclo oxygenase 2 products like Prostagladins D_2,F_2 and Thromboxane A_2 causes bronchoconstriction whereas Prostaglandin D_2 enhances constrictor action of histamine in asthmatics . Prostaglandin E2 and prostacyclins have bronchodilator and anti inflammatory activity.

Activation of 5-lipoxygenase by arachidonic acid pathway results in the synthesis of Leukotrienes B4, C4, D4 and E4. They are not preformed mediators.Leukotriene B4 is a neutrophilic chemoattractant. Leukotrienes C4, D4 and E4 are bronchoconstrictors, enhances hyperresponsiveness of the airways, facilitates microvascular leakage and enhances secretion. of mucus in the airways.

Platelet-activating factor is synthesized by inflammatory macrophages and granulocytes which causes bronchoconstriction and mucus secretion. It's unique role in asthma is controversial. It induces leakage from the microvessels. It's inflammatory role along with other mediators, in the late asthmatic phase results in recruitment and degranulation of eosinophils.

Cytokines, interferons and growth factors are secreted by inflammatory macrophages. They help in the immune and inflammatory processes by recruitment of inflammatory cells, amplification and ultimately its cessation. They also help in the regulation of repair responses and in restoring the tissue integrity. They are the key mediators in the chronic inflammatory process of bronchial asthma.

Endothelins are potent vasoconstrictors and bronchoconstrictors. They are responsible for proliferation of smooth muscle cells in chronic asthma. Nitric oxide is a potent vasodilator and bronchodilator that antagonises endothelin. They also provide free radicals which are responsible for on going tissue damage. They help in the amplification of Th_2 cells in immune response and increases microvascular leakage.

Growth factors play an important role in the chronic inflammatory process by proliferation of smooth muscle cells and remodelling of vasculature. Proliferation of fibroblasts and secretion of collagen is due to the effect of growth factors like fibroblast growth factor (FGF) ,Platelet-

derived growth factor and Transforming growth factor b(TGF-b). Fibrosis of subepithelium is due to the thickening of basement membrane from deposition of collagen by growth factors.

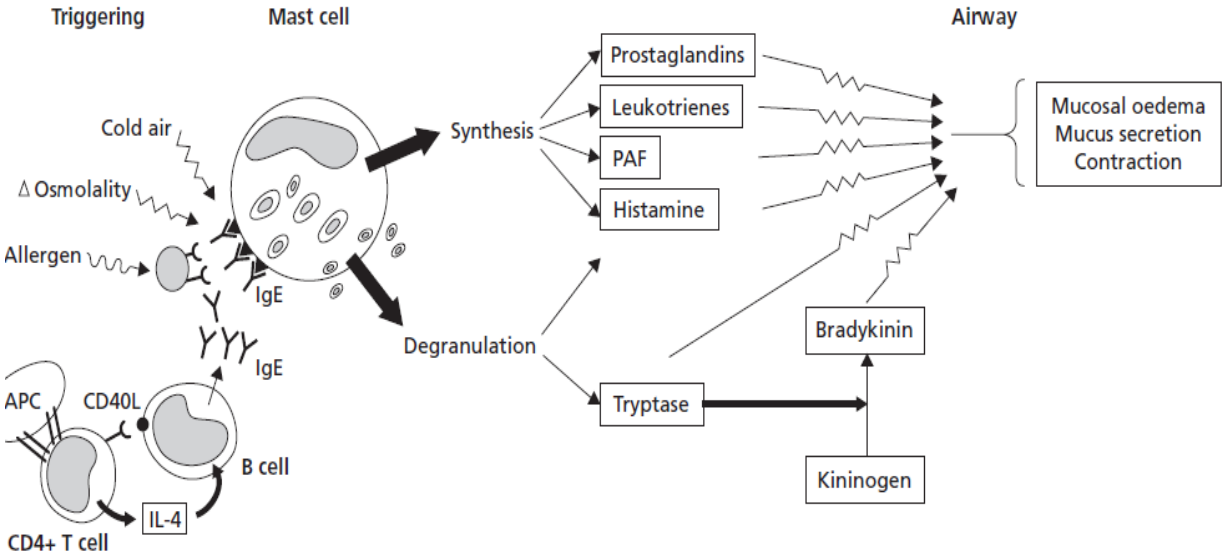
Chemokines have chemoattractant property. C-X-C on chromosome 4 is a neutrophilic chemoattractant. Platelet factor 4 is not a chemoattractant. Interleukin8 is specifically chemotactic for neutrophils.It is also an eosinophilic chemoattractant in the presence of Interleukin-4 .The genes encoding the CC chemokine on chromosome 16(Regulated upon Activation Normal T cell Expressed and presumably Secreted) is an eosinophilic chemoattractant. Macrophage derived chemokine (CCL-22) is involved in chemoattraction of helper 2 T cells.

Events in the pathogenesis[8].

Early asthmatic response -Mast cells are triggered by cold air,changes in the osmality of tissue fluid and exercise. Allergens attach to the surface of mast cells via Ig E receptors(FceR1).Antigen presenting cells activate T lymphocytes which secrete Ig E which also triggers mast cells. After triggering , mast cells undergo degranulation and synthesise prostaglandins, leucotrienes, PAF, Tryptase which result in mucosal edema, mucus secretion and bronchoconstriction.

PATHOGENESIS

EARLY ASTHMATIC RESPONSE



2. Late asthmatic response-Inflammatory cells and immune cells are responsible for the effects of inflammatory response. It comprises two phases 1.cell recruitment phase 2.effector mechanism phase.

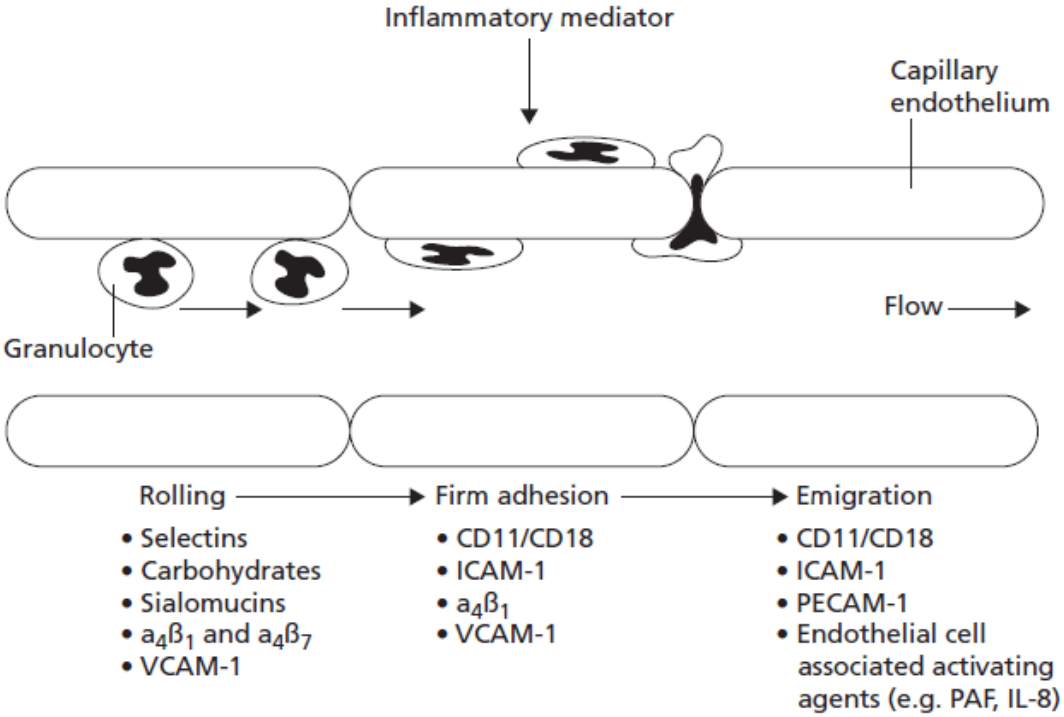
1. Cell recruitment phase-Recruitment of neutrophils into challenged airway, followed by recruitment of eosinophils and monocytes by means of chemotactic factors and chemotactic chemokines. Transmigration of granulocytes occurs as a multistep process, transient adhesion of granulocytes via adhesion molecules of selectin family and tight adhesion via integrin family (ICAM-1&VCAM-1) followed by transmigration and emigration of granulocytes into endothelial cells of microvessels . The

usefulness of selective adhesion molecules is that it is responsible for the specific accumulation of eosinophils in response to allergy and also for the variable timing of recruitment of inflammatory cells to the inflammed site (monocytes and eosinophils preceeded by neutrophils).

After recruitment these cells secrete histotoxic granules which produce endothelial injury, which contributes to the various effects of inflammatory response. They can also release wide range of ROI including O_2^-, H_2O_2 and radicals of OH groups and secretes leukotrienes and prostanoids that causes increased mucus secretion, mucosal oedema and narrowing of the airways. This reaction is responsible for irreversibility of bronchodilation. Recent studies show that basophils rather than eosinophils are of importance in mediating the late phase response.

LATE ASTHMATIC RESPONSE

CELL RECRUITMENT PHASE-I



PHASE-II INFLAMMATORY RESPONSE AND ASTHMA EFFECTOR MECHANISMS.

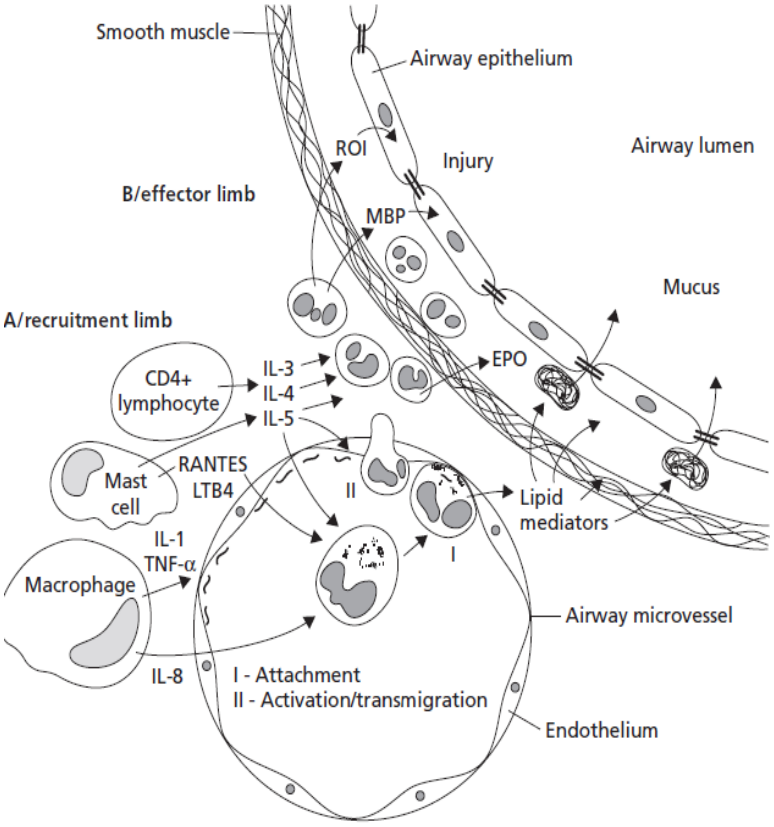


Fig. 33.6 Inflammatory response and asthma effector mechanisms. ROI, reactive oxygen intermediate.

Effects of inflammatory response[8]

1.Vascular responses

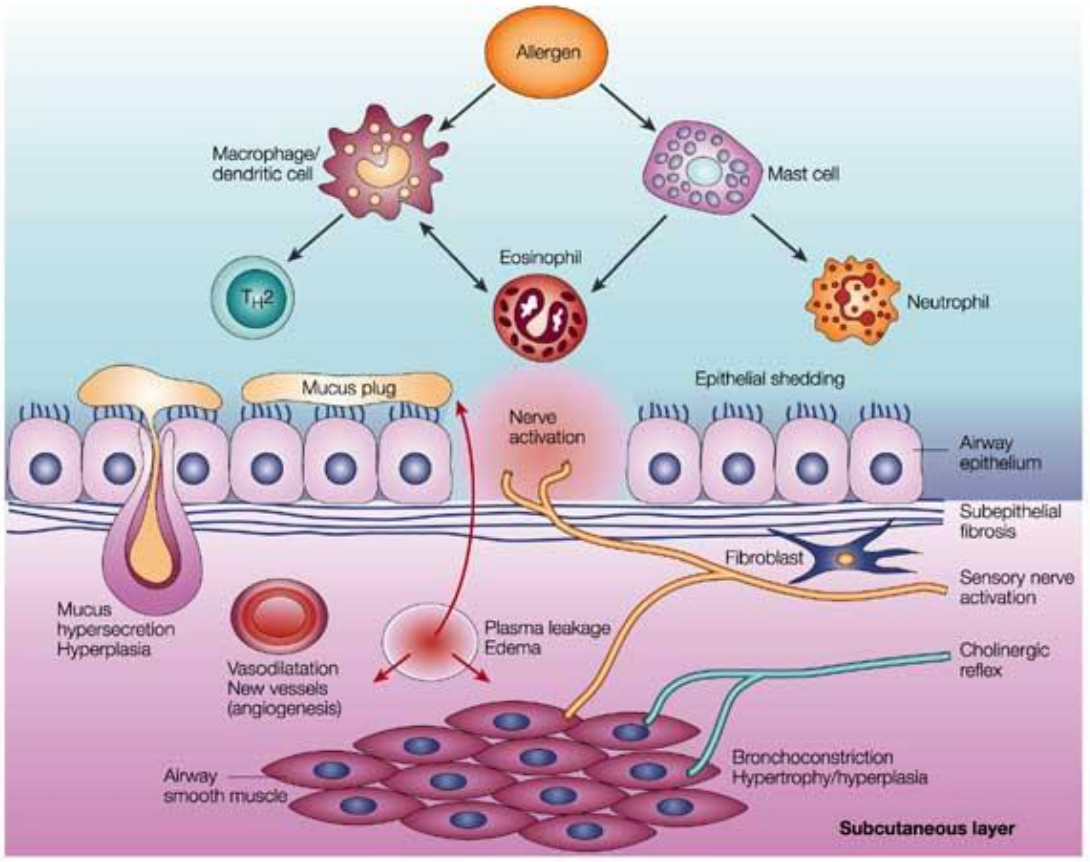
Swelling of the mucosal membrane is responsible for increased narrowing and resistance of the airways. This inflammatory response is due to mediators causing increased vascular permeability and exudation of plasma into the airway lumen. Increased blood flow in the bronchial arteries is due to angiogenesis by inflammatory mediators like growth factors (VEGF, FGF, PDGF) and cytokines (Interleukin 1 and 8) which result in reduction in the airway calibre. Remodelling of the airways in chronic severe asthma may also be due to angiogenesis. Increased blood flow may help in removing inflammatory mediators from the airway. It may also be involved in the development of exercise-induced asthma .

2. Epithelial injury and Shedding-

Epithelial desquamation or denudation is a pathologic feature of asthma. It ranges from mild epithelial shedding to extensive denudation. On exposure to asthmatic triggers, it may lead to epithelial injury. It is mainly due to O_2^-,H_2O_2, OH groups produced by the inflammatory cells and granular enzymes. Shedding of epithelium contributes to hyper responsiveness of airways. Epithelial damage which allows penetration of allergens; loss of enzymes neutral endopeptidase that degrade certain

peptide containing inflammatory mediators; loss of epithelial-derived relaxant factor and exposure of sensory nerves in the airways leads to reflex neural effects on the airways.

PATHOPHYSIOLOGY OF ASTHMA



4. Fibrosis

Subepithelial fibrosis is not only due to thickening of basement membrane but also due to deposition of types III and V collagen below the true basement membrane and is associated with eosinophil infiltration. The release of profibrotic mediators like TGF causes inflammatory infiltration which results in irreversible narrowing of airways.

5.Mucus Hypersecretion

Increased mucus secretion by IL-4 and IL-13 contributes to the viscid mucous plugs that occlude asthmatic airways. Hyperplastic submucosal glands in the large airways and hyperplastic goblet cells in the epithelium are responsible for increased secretion of mucus. Airway mucus is composed of Charcot Leyden crystals, creola bodies, albumin and mucin glycoproteins.

6. Airway Smooth Muscle

The abnormalities of smooth muscle in the airways may be due to the chronic inflammatory process. Inflammatory mediators are responsible for the regulation of resting membrane potential by modulating ionic channels in the smooth muscle cells of peripheral airways. Thus it alters the level of excitability of these cells. Protein kinase C is activated by the inflammatory mediators in the airway smooth muscle cells. Down regulation of beta

adrenergic responses in airway smooth muscle is due to the G- protein phosphorylation coupling of beta receptors to adenylyl cyclase.

There is also a characteristic hypertrophy and hyperplasia of airway smooth muscle in asthmatic airways, as a result of stimulation of airway smooth-muscle cells by various growth factors such as platelet-derived growth factor (PDGF) or endothelin-1 released from inflammatory or epithelial cells.

7. Neural Effects

Defect in efferent (autonomic) nerve control leads to Airway hyperresponsiveness. Cholinergic pathways, through the release of acetylcholine acting on muscarinic receptors causes bronchoconstriction. Inflammatory mediators may activate sensory nerves, resulting in reflex cholinergic bronchoconstriction or release of inflammatory neuropeptides. Inflammatory products may also sensitize sensory nerve endings in the airway epithelium such that the nerves become hyperalgesic. Neurotrophins, released from different cells in the airways, including epithelial cells and mast cells, may cause proliferation and sensitization of airway sensory nerves. Airway nerves may also release neurotransmitters, such as substance P, which have inflammatory effects.

Nuclear factor kappa B (NF-kB) is the factor responsible for transcription which plays a major event in bronchial asthma. Various stimuli can activate this factor, like the activators of protein kinase C,Interleukin-1b and TNF-alpha (They are the cytokines which have an action on proinflammation) and oxidants. It is the major factor of transcription which regulates the expression of inducible form of nitric oxide synthase, selectin and integrin groups, cytokines of proinflammation like Tumour Necrosis Factor-alpha,Granulocyte Monocyte Colony Stimulating Factor, Cyclo oxygenase-2 and neutrophilic chemokines like Interleukin 8,Macrophage Inhibitory Protein -1a and eosinophilic chemokines. The above mentioned factors are the amplifiers of inflammation.

PHYSIOLOGIC DISTURBANCES

The disturbances in function are most clearly caused by narrowing of the airways. This narrowing is diffuse, affecting all levels of the tracheobronchial tree. Tests of airway function are abnormal. The resistance to the airflow is increased and maximal flow during expiration is also decreased at all levels. Maximal inspiratory flow is also reduced. Residual volume of the lung is increased due to the premature closure of peripheral bronchioles at increased lung volumes. The adaptive advantages of breathing at higher lung volumes are increase in the circumferential

traction—or "tethering" force—on intrapulmonary airways, tending to hold them open, and an increase in the elastic recoil of the lungs, increasing the driving pressure for expiration. The work of breathing is increased because of the narrowing of the airways , decreased compliance of the lungs and increase in thoracic cage volume.

This increased work must be performed by muscles of breathing - the diaphragm and intercostal muscles- and the accessory muscles (e.g., the sternocleidomastoids) are also brought into play. Fatiguability occurs due to increased breathing and this inappropriateness of the length-tension relationship in the muscles of breathing is perceived as dyspnea.

The airway narrowing in asthma also affects gas exchange. The obstruction of airways is not similar throughout the airways .Shifts in pulmonary blood flow cannot completely compensate for the underventilation of the regions of lung subtended by the most obstructed airways. The resulting ventilation perfusion mismatch widens the alveolar-arterial oxygen difference [(A - a) P_{O_2}], and arterial oxygen tension in patients with acute severe asthma typically ranges between 60 and 69 mmHg.

CLINICAL FEATURES

The cardinal triad of bronchial asthma is chest tightness, wheezing, and shortness of breath on exposure to triggering factors, varying from day to day, within a day, with symptoms worsening at night. Throat tightness, choking, sniffed chest and chest congestion indicate the severity of bronchoconstriction. Non productive cough, nocturnal and chronic cough are also produced and worsened by triggers of asthma.Sputum production may also occur.

Physical Examination

Polyphonic expiratory wheeze is the most characteristic finding of asthma reflecting turbulent air flow in peripheral airways. Overinflation of thoracic cage results, due to adaptive response of breathing. Swelling and pallor of nasal mucosa indicate allergic rhinitis. Nasal polyps occurs in adult onset asthma. Sinus tenderness and purulent discharge indicates sinusitis. Obesity in addition reduces functional residual capacity.

Course of illness

Disease persistence and progression is mainly due to chronic inflammatory process. Inspite of anti-inflammatory therapy eosinophilic infiltration and remodelling of the bronchial epithelium contributes to the persistence and progression of disease. Even in the quiescent phase, helper T_2 cells in the airways are active. Activation of Transforming growth factor

Beta by metalloproteinases which stimulates IL-13 to promote fibrosis is also responsible for epithelial injury,eosinophilia and secretion of mucus. It is the key effector cytokine in asthma. The inflammatory response is augmented by Interleukin-13 and other Th2 cytokines produced by non-T cells .Amplification of inflammation is by the cytokines, proteases and chemokines which are derived from fibroblasts, smooth muscle and local epithelial responses .Adenosine produced by the injured cells enhances IL-13 production[9].

Factors important for persistence and progression of asthma are[10]

1. Sex

It shows significant relation to the deterioration of pulmonary function in patients with persistent asthma. The severity of asthma is more in females due to the frequent hospital admission and prolonged hospital stay during an acute attack. Poor prognosis is common in females. Young females are more prone for Non atopic asthma.

2. Smoking

Passive exposure to cigarette smoke in childhood is a risk factor for wheezy bronchitis, airway hyperresponsiveness, and symptomatic asthma. Active smoking was a predictor of lower FEV1 % in early adulthood in patients with nonatopic asthma. In adults, the rate of decrease in lung

function over time, as measured by FEV1is greater in those with asthma than in healthy subjects. Moreover, the rate of decrease among smokers is greater in those with asthma than in those without asthma.

3. Age of onset

Respiratory symptoms occuring for the first time at an older age had a good prognosis as indicated by Forced Expiratory Volume in 1 second in children with non atopic asthma .In contrast ,no such relation exists in atopic asthma.

4. Duration of Illness

Increased airway vulnerability due to unopposed inflammation play a unique role in the deterioration of pulmonary function in recently diagnosed asthma. In chronic cases, chronic inflammatory process leads to decline in the lung function due to progressive airway remodelling.

5. Atopy

In non atopic asthmatic population, chronic inflammation is considered to be one of the risk factor in the decline of lung function. Several follow up studies in atopic asthmatic individuals show that there is a negative relationship between atopy and outcome of lung function. Chronic inflammatory process is responsible for the progression of disease irrespective of atopic status.

6. Severity of symptoms

Severe persistent asthma and increased frequency of symptoms are associated with decline in lung functions like Forced Expiratory Volume in 1second and Forced Expiratory Volume in1 second /forced vital capacity ratio. Several studies have concluded that both the severity and frequency of illness are associated with a poor prognosis in asthmatic individuals. Growth of the individual is also affected by this.

6. Level of Lung Function

Initial (prior to diagnosis) decline in the pulmonary function is an indicator of further deterioration of pulmonary function. Low level of lung function is an independent factor for disease progression in asthma.

7. Airway hyperresponsiveness

Bronchial hyperresponsiveness is one of the factors responsible for inflammatory response in asthma. Hyperresponsiveness of bronchial airways predicts low levels of FEV1 in adolescent individuals .This was observed in population studies. Thus airway hyperresponsiveness is associated with both impaired attainment of pulmonary function in children and accelerated deterioration of pulmonary function in adults.

8. Response to Bronchodilators

The most important characteristic feature of asthma is positive reversibility test. It occurs with beta $_2$ agonist (broncho dilators). Excess response to bronchodilators is one of the risk factors for worst outcome.

9. Blood Eosinophilia

Presence of eosinophila, eosinophilic cationic protein and IL-5 in the peripheral blood are related to the severity of presenting asthma and denotes an unfavourable outcome with respect to decline in lung function in asthmatics.

10. Daily secretion of mucus for more than three months in one year for at least two consecutive years indicates chronic inflammatory process in the airways. Prolonged periods of hypersecretion of mucus in asthmatic individuals lead to an accelerated deterioration of pulmonary function.

11.Anti inflammatory Drugs

Minimizing the degree of airway inflammation may lead to a more favourable growth of lung function in children with asthma. Anti-inflammatory therapy, especially treatment with inhaled corticosteroids, not only effectively improves the clinical severity of asthma but also reduces the chronic inflammation in the airways of asthmatic patients.

Classification of asthma

Assessment of severity and clinical pattern of asthma is needed in recently diagnosed asthmatic patients to initiate the treatment and to decrease exacerbations.

A recently diagnosed asthmatic patient is classified according to:

- the frequency and severity of symptoms
- spirometric assessment and reversibility with bronchodilators.

Intermittent asthma

- Asthmatic symptoms occurs weekly once during morning hours.
- Asthmatic symptoms occurs monthly once in nocturnal period.
- Acute episodes occurs infrequently and for short periods.
- Forced Expiratory Volume in1second is at least more than eighty percent of predicted and varies by less than twenty percent.

Mild persistent asthma

- Asthmatic Symptoms occurs more than twice a week during morning hours but not every day.
- Asthmatic symptoms occurs more than twice a month in nocturnal period, but not every week.
- Acute episodes occur occasionally and may affect activity or sleep.

- Forced Expiratory Volume in one second is at least Eighty percent predicted and the variability by twenty to thirty percent.

Moderate persistent asthma

- Asthmatic symptoms occurs every day during daytime, but do not affect regular activity.
- Asthmatic symptoms occur once a week in nocturnal period.
- Acute episodes occurs occasionally and can affect regular activity.
- Forced Expiratory Volume in one second is sixty to eighty percent predicted and the variability is more than thirty percent .

Severe persistent asthma

- Asthmatic symptoms occurs daily during morning hours and affect day to day activity.
- Asthmatic symptoms occurs daily in nocturnal period.
- Acute episodes occur frequently.
- Forced Expiratory Volume in one second is sixty percent or less than predicted , and the variability is more than thirty percent.

Complications

1. The most common complication is due to long term steroid use. Esophageal candidiasis is a common side effect of inhaled corticosteroids therapy.

2. Infections continue to irritate the damaged lung airways,causing it to swell and produce more mucus. Illnesses such as bronchitis, pneumonia, tuberculosis, compounded with asthma can be a deadly combination. H1N1, seasonal influenza, avian influenza, and RSV can also be a deadly mix**.** Allergic bronchopulmonary aspergillosis (ABPA) occurs in patients with asthma resulting in pulmonary infiltrates, thick mucus plugs that contain hyphae of Aspergillus fumigatus, elevation of total serum IgE concentration and peripheral blood and sputum eosinophilia[17].

3. Breathing disturbances lead to night awakening, signs of snoring and sleepiness during the daytime. Another problem with asthmatics is that they develop sleep apnea due to irregular breathing pattern.

4. Pneumothorax is a condition where air leaks out of the lungs. In asthma, it may be caused by the rupture of overstretched alveoli or air sacs in the lungs. Pneumomediastinum may be suspected in an asthma patient who complains of substernal chest pain during an asthma attack and having subcutaneous emphysema in the neck and chest and with Hamman's sign on auscultation[18].

5. Segmental collapse of lung occurs due to impacted mucus plug[20].

6. Severe coughing episode may lead to a fractured rib, urinary incontinence in women and fecal incontinence in men or women.

7. Long-standing chronic severe asthma occasionally leads to development of pulmonary hypertension and corpulmonale, and chronic hypercapnia.

8. Status asthmaticus is a life threatening complication of asthma.

Status asthmaticus is an acute exacerbation of asthma that does not respond to standard treatment with bronchodilators and steroids and is associated with symptoms of potential respiratory failure. Poor control of allergens or asthma triggers in the home and/or workplace ,post viral infection, exercise in a cold environment, poor adherence to anti-inflammatory therapy are the risk factors for this attack. Small bowel infarction with pneumatosis intestinalis occurs in the early course of life-threatening severe acute asthma[19].

Levels of severity of acute asthma exacerbations [11]

Moderate asthma with exacerbation-

- Increasing asthma symptoms
- Peak Expiratory Flow Rate more than Fifty to seventy percent.

- No features suggestive of increased severity of asthma.

Acute severe Asthma-

- Peak Expiratory Flow Rate Thirty three to Fifty percent of best or predicted
- Respiratory rate more than twenty five per minute.
- Heart rate more than one hundred and ten per minute.
- Patient is not able to complete sentences in one breath

Life threatening Asthma

The clinical features are as follows

Signs of manifestations	**Measurements**
Altered mental status	Peak Expiratory Flow rate less than thirty
Fall in Blood pressure	three percent of best or predicted
Cyanosis	Oxygen saturation less than ninety two percent
Silent chest	Pa O2 less than 8 kPa
Increase in heart rate	"Normal" Pa CO2 (4.6–6.0 kPa)
Poor respiratory effort	
Exhaustion	

Near-fatal asthma

- Partial pressure of carbondioxide is increased.
- It requires life saving measures like mechanical ventilation with increased inflation pressures.

Treatment

1. Oxygen –Six to eight Litres /min of high flow oxygen is necessary and is monitored by pulse oximetry. In severe attack, it is necessary to monitor arterial Pa $O_{2,}$$PaCO_2$, pH and $SaO_{2.}$
2. Beta 2 agonists – beta 2 agonists have a unique role in relieving the clinical symptoms and improving the lung function in acute episodes. 1- 2 mL of salbutamol solution (each ml contains 5 mg of salbutamol) with 2 mL of saline via nebuliser is necessary. Frequency of dosing will depend upon clinical response, and if there is no response, the dose is to be titrated.A dose of 12 puffs (via MDI with Spacer) is equivalent to a 5 mg nebulised salbutamol.Intravenous route in status asthmaticus is controversial.
3. Nebulised ipratropium bromide –Combination therapy of 500 µg of ipratropium bromide with salbutamol via nebuliser for every 2 hours is recommended for severe attacks.
4. Systemic steroids - 250 mg of IV hydrocortisone is to be given as a starting dose followed by 250mg sixth hourly for the first twenty four

hours. In moderate attack one milli gram per kilogram body weight of prednisolone can be given orally and in a mild attack oral steroids can be given.

5. IV aminophylline – The role of this drug in acute asthma is controversial.

6. Adrenaline –In anaphylaxis adrenaline 0.5 mL of one in one thousand dilution can be given by intramuscular route. In case of respiratory arrest five milli litre of one in ten thousand dilution can be given slowly by intravenous route.

There is no further clinical evidence to support the use of other emergency therapeutic measures like heliox for nonintubated patients. The role of noninvasive procedures like positive pressure ventilation in patients with status asthmaticus[12]is controversial .Further studies are needed for these.

Differential Diagnosis

1. Vocal cord dysfunction[21] is due to abnormal vocal cord adduction during inspiration. It may disappear with panting, speech, or laughing. Patients present with chronic symptoms suggestive of asthma, normal spirometry, poor response to asthma medications. The diagnosis can be

made using direct laryngoscopy but only during symptomatic periods or after exercise.

2. Tracheal and bronchial lesions-Airway tumors (endobronchial carcinoid and mucoepidermoid tumors) are reported to manifest with symptoms similar to those of asthma and may be differentiated by persistence of symptoms; and associated voice changes, haemoptysis or weight loss .On physical examination a fixed monophonic inspiratory wheeze or stridor is heard. Other tracheal lesions include bronchocentric granulomatosis, subglottic stenosis, subglottic web, tracheal hamartoma, bronchogenic cysts, leiomyoma, and tracheobronchopathia osteoplastica.

3. Aspiration of foreign body can cause both focal and generalised wheeze. It occurs in children and in middle aged people.

4. Pulmonary embolism, pulmonary infiltrates with eosinophilia, drug intake (ACE inhibitors) may mimic bronchial asthma.

5. Pulmonary migraine occurs due to the obliteration of lobar bronchus. It is characterised by migraine headache, recurrent attacks of asthma and atelectasis. In case of atelectasis of unknown eliology, pulmonary migraine should be thought of.

6. Congestive heart failure is characterized by dyspnea not preceeded by cough, presence of S_3, basal rales and wheezing. It occurs due to dilatation

of pulmonary vasculature and edema of the intersitium which causes decline in the compliance of lung which leads to symptoms like asthma. In cardiac asthma wheezing occurs intermittently and during night time due to the spasm of bronchioles.

7. Diffuse panbronchiolitis may mimic symptoms of bronchial asthma like coughing, dyspnea on exertion,wheezing and sinusitis. High-resolution CT is usually done to differentiate it from asthma.

8. Sinusitis in toddlers, can be associated with the symptoms of asthma

9. Gastroesophageal reflux (GER) may mimic asthma symptoms like dry cough, recurrent bronchitis, pneumonia, wheezing, and asthma.

10. Anomalies of arch of aorta can occur in middle age period which may simulate exercise-induced asthma.

11. Endobronchial tuberculosis simulating symptoms of bronchial asthma.

12 Extrinsic conditions like mediastinal lymphadenopathy from Hodgkins lymphoma can contribute to symptoms like asthma.

Aspirin or NSAID hypersensitivity and reactive airways dysfunction syndrome may be mistaken for asthma.

Though COPD closely mimics asthma, reversibility test differentiates it from asthma. A significant smoking history greater than 20-

pack years should strongly favour chronic obstructive pulmonary disease (COPD) rather than asthma.

Obstructive and restrictive lung diseases share the same main clinical features. They are identified using pulmonary function tests, Chest X-ray and CT scan of the chest.

Investigations-

1. Blood eosinophil count- To exclude tropical pulmonary eosinophilia.
2. Sputum for AFB and Eosinophil : To exclude pulmonary tuberculosis and pulmonary eosinophilia. Sputum for Churchman's spirals (mucous that forms a cast of the small airway) and for Charcot Laden crystals (breakdown products of eosinophils)
3. Blood glucose to exclude Diabetes mellitus.
4. ECG/Echocardiography to exclude cardiac diseases.
5. Chest X-ray P/A view :usually normal in asthma. To exclude COPD, Pulmonary tuberculosis, Consolidation, Pneumothorax, Pulmonary oedema, Tumor, FB in airway etc.
6. Blood gas analysis- At the beginning of an asthmatic episode there is a fall in the partial pressure of oxygen and carbondioxide but the pH rises. Due to the deterioration from the disease the partial pressures of oxygen and carbondioxide fall continuously whereas the pH rises .

At one stage the lungs are not able to wash out the carbon dioxide and then the partial pressure of carbon dioxide and pH start rising but the partial pressure of oxygen falls continuously. As the disease becomes very worse the partial pressure of carbondioxide and the increased pH comes back to their normal level.

7. **S**kin hypersensitivity test - To determine the cause of asthma.
8. Blood Ig E →Extrinsic Asthma, Blood Ig A → Intrinsic Asthma andaspergillus Ab.

9. Pulmonary Function Test

Pulmonary function tests are a group of procedures that measure the function of lung (inhalation and exhalation of air and exchange of gases).These tests can measure response to bronchodilators, examine the effect of exercise, and measure variability over a period of days or weeks, with or without a course of steroids and assess the effect of challenge testing. It can demonstrate an obstructive pattern, the hallmark of which is a decrease in expiratory flow rates : reduction in forced expiratory volume over 1 sec (FEV_1) and a proportionally smaller reduction in the forced vital capacity (FVC) and decreased FEV_1/ FVC ratio (generally <0.70). The clinical diagnosis of asthma is supported by an obstructive pattern that

improves after bronchodilator therapy. Zang M, et al reported that symptoms, FEV1/FVC, and peak flow are indices of the control of asthma.

Peak flow meter

It is a instrument of portability that measures maximum speed of expiration (peak expiratory flow rate). The peak expiratory flow rate is the maximal rate at which a person can exhale during a maximal expiratory effort after a deep inspiration. In patients with asthma, the PEFR percent predicted correlates well with the percent predicted value for the forced expiratory volume in one second (FEV1). It can help recognize early changes (often hours or even days) before the signs of worsening asthma show.

PEAK FLOW METER

Merits of Peak Flow Meter:

- Identification of asthma severity.

- During an exacerbation ,to check the therapeutic response.
- The therapeutic response of chronic asthma can be monitored by the course of disease. It provides information regarding changing of treatment.
- It identify the worsening of pulmonary function and avoid frequent exacerbation.

A Peak Expiratory Flow Rate lower than predicted level indicates narrowing of airways or a decline in the volume of lung . These features are the characteristic features of obstructive lung disease.

Bronchial asthma is confirmed by

- Test of reversibility.
- Variability of Peak Expiratory Flow Rate in a day is greater than twenty percent.
- After running or exercise the decremental response of peak expiratory flow rate is fifteen percent or greater.

The variability of Peak Expiratory Flow Rate is the difference between the highest and lowest value in twenty four hours. The lowest values of Peak Expiratory Flow Rate is expressed in percentage . Diurnal variability of Peak Expiratory Flow Rate is common. The highest level of Peak Expiratory flow rate usually occurs in the afternoon and the lowest

level in the early morning hours. A variability of Peak Expiratory Flow rate more than twenty percent is the diagnostic feature of asthma. A higher variability of Peak Expiratory Flow Rate indicates an increase in severity of asthma .Rise in peak Expiratory flow rate more than twenty percent after the administration of bronchodilator indicates positive reversiblity test. It is a diagnostic test of bronchial asthma and has been reported in the study of Dekker et al[14].

Procedure : Blow into the Peak Flow Meter with force. This is repeated thrice and the best reading is to be recorded.

The Steps are as follows-

- The Device should read zero or be at base level before the procedure.
- Standing up (unless you have a physical disability)position is best for doing the procedure.
- The breath is to be taken as deep as possible
- The meter is to be kept in mouth and lips to be closed around the mouthpiece
- Air to be blown out into the meter as quick and hard as possible for1 to 2 seconds
- Coughing, spitting or tongue itself can block the mouthpiece
- The readings are to be recorded.

• The procedure is to be repeated two times, and the highest of the three values is to be recorded.

According to the American Lung Association the readings of peak flow meter are classified into three zones. Asthma management plan is based on these three zones.

Green zone:

Peak Expiratory Flow Rate is eighty to hundred percent of personal best. It indicates that the asthma is under good control.

Yellow zone:

Peak Expiratory Flow Rate is Fifty to Eighty percent of personal best. It indicates caution. It means respiratory airways are narrowed and additional medication may be required.

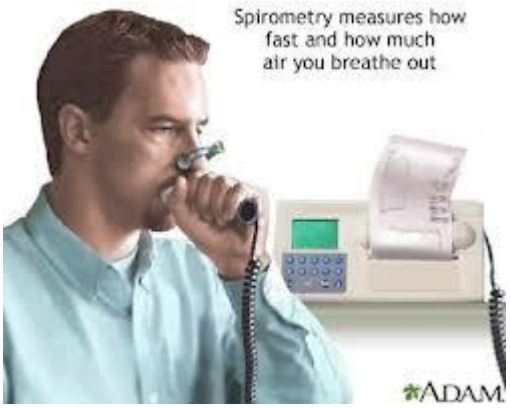
Red zone:

Peak Expiratory Flow Rate below Fifty percent of personal best. It indicates a medical emergrncy.Severe airway narrowing may be occurring and immediate action is to be taken.

Spirometry[13] (meaning the measuring of breath) is the most common of the pulmonary function tests (PFTs), measuring lung function, specifically the amount (volume) and/or speed (flow) of air that can be inhaled and exhaled as demonstrated by kath Cooper et al.

The more common lung function values measured with spirometry are Forced vital capacity (FVC), Forced expiratory volume (FEV), Forced expiratory flow 25% to 75%,Peak expiratory flow (PEF),Maximum voluntary ventilation (MVV),Slow vital capacity (SVC) Total lung capacity (TLC), Functional residual capacity (FRC),Residual volume (RV). Expiratory reserve volume (ERV).

SPIROMETRY



Preparation Before the test

1. Refrain from smoking within 1 h of testing
2. Avoid consuming alcohol within 4 h of testing
3. Avoid performing vigorous exercise within 30 min of testing
4. Avoid wearing clothing that substantially restricts full chest and abdominal expansion
5. Avoid eating a large meal within 2 h of testing
6. Wear denture if you have it.

According to British Thoracic Society in 1994

The procedure is as follows:

1. The individual to be seated in an armed chair.
2. At the beginning, 2 values of vital capacity in relaxed position to be tested succeeded by 3 FVC values. Leakage of air is prevented by using nasal clips.
3. The individual is instructed to take a deep breath before the procedure.
4. To prevent air leakage, tight sealing of instrument is to be done.
5. The vital capacity can be measured in two ways. In relaxed position, the individual to breath out in a slow speed. This gives the measurement of

relaxed Vital Capacity. For Forced Vital Capacity, before the test the individual should inspire completely and then should blow out fast, hard and continuously in order to exhale all the air.

6. It will take 6s to do FVC, But it can take up to 15s in some patients with obstructive breathing patterns ; Leave at least 30s between the blows for the recovery of the individual. At one time the individual can try three to eight blows.

Select the best results of FEV1 and FVC from three reproducible blows. Calculate the FEV1/FVC ratio from the best VC reading.

FEV1-The amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation. It is reduced in both obstructive and restrictive disease. mild: $FEV_1 \geq 80\%$ predicted; moderate: FEV_1 50 to <80% predicted; severe: FEV_1 30 to <50% predicted; very severe: FEV_1 <30% predicted.

Reversibility is demonstrated by a >12% and 200-mL increase in FEV_1 15 minutes after an inhaled short-acting Beta $_2$-agonist or 2 to 4 week trial of oral corticosteroids (OCS) (prednisone or prednisolone 30–40 mg daily).

FVC- The amount of air forcibly exhaled from the lungs after the deep inspiration. FVC is usually normal in obstructive disease and

decreased if there is trapping of air. FVC is decreased in restrictive disease. Forced Expiratory Ratio is the percentage of forced Vital Capacity expelled in the first second of a forceful expiration. In restrictive disease it is usually within normal limits and decreased in obstructive disease.

The flow-volume loop (also called a spirogram) is a plot of inspiratory and expiratory flow (on the Y-axis) against volume (on the X-axis) during the performance of maximally forced inspiratory and expiratory manoeuvres. It is not considered as a primary diagnostic aid.

Provocative Test

Challenge tests are the provocative measures to identify the responsiveness of bronchial airways by inhaling the substances causing the symptoms of asthma. During this procedure, inhalation of substance occurs via nebulizer. The substances are delivered in aerosolised form through the face mask or mouth piece. Substances like methacholine or mannitol can be used. The measurements are recorded by spirometry to evaluate pulmonary function prior, during and after the procedure.

Stress tests are done to assess the effect of stress like exercise on pulmonary function tests. The values are recorded by spirometer after the stress test and then again at resting state.

Treatment

Aims of Asthma Therapy

1. Chronic symptoms to be minimal including nocturnal

2. Minimal exacerbations.

3. No emergency visits.

4. Use of beta$_2$-agonist to be minimal

5. No limitations of activities, including exercise.

6. Peak expiratory flow circadian variation <20%.

7. Normal PEF

8. Minimal adverse effects from medication.

Approach to management

i. Education of patient and family

ii. Avoidance of precipitating factors

iii. Use of the lowest effective dose of convenient medications minimising short and long term side effects.

iv. Assessment of severity and response to treatment

1. Education of patient and family

Ensuring the patient's cooperation and compliance with therapy, avoidance of triggers, proper use of inhaled drugs, proper use of peak flow meter, recognition of features of worsening asthma and side effects of drugs.

2. Lifestyle modification

Avoidance of triggers is a key component of improving control and preventing attacks (smoking, aspirin, beta blockers, NSAID, allergen, occupation, atmospheric pollution, food, exercise and cold air).

3. Medications-

The main drugs for asthma can be divided into bronchodilators, which give rapid relief of symptoms mainly through relaxation of airway smooth muscle and anti inflammatory drugs which inhibit the underlying inflammatory process.

There are three classes of bronchodilators currently in use:$beta_2$-adrenergic agonists, anticholinergics, and theophylline. Of these, $beta_2$-agonists are by far the most effective.

Bronchodilators

Short-acting bronchodilators are also called "quick-acting," "reliever," or "rescue" medications. These medications relieve symptoms of acute exacerbation.. They are salbutamol, terbutaline and fenoterol. The long-acting bronchodilators can be used twice daily to control asthma. They do not give quick relief in acute exacerbation. They should be used only in combination with inhaled steroids for long-term control of asthma

symptoms. They are salmeterol and formoterol. Bronchodilators (Beta 2 – agonist) act on bronchial smooth muscle and reverse bronchoconstriction, inhibits mast cell mediator release,inhibits plasma exudation and airway edema,increased mucociliary clearance,decrease mucus secretion, decrease cough and have no effect on inflammation.Mode of delivery is by oral/inhalation. Oral forms of bronchodilators have more systemic absorption compared to inhalers and they tend to have more systemic side effects.

Contrary to this, bronchodilators delivered with inhalers enter directly into the peripheral airways rather than systemic circulation and have fewer side effects. Regular treatment with bronchodilators is to be avoided because of increased development of bronchial hyper responsiveness. Asthma severity can be identified by the response to treatment. If there is no response to using a Beta 2 –agonist more than thrice a week, it is indicated to start treatment with corticosteroids.

Inhalation is either by nebulisation or metered- dose inhaler and spacer. Nebulizers are devices that have the capacity to change the medications from liquid into fine moist form which is easier for deposition of medication in the peripheral airways.

The nebulizers are of 2 types

1. Jet nebulizers

2. Ultrasonic nebulizers.

NEBULISER

• Jet nebulisers pass compressed air through the medication to convert it into a mist.

• Ultrasonic nebulisers pass ultrasound waves through the liquid medication to convert it into a mist.

Metered- dose inhaler is a hand-held pressurised canister that delivers a mist of aerosolised medication to the lungs. It is an inexpensive and effective method in treating bronchial asthma. The significant advantages of aerosol drug delivery are quicker onset of pharmacological action, since the drug is being delivered to the peripheral airways[15], the site which needs therapeutic effect and a lower systemic bioavailability, which decreases systemic adverse effects.

A spacer is an external device that is attached to an MDI.

METERED DOSE INHALER AND SPACER

Advantages of MDI

1. It allows better drug delivery by enhanced actuation.
2. It facilitates the coordination of inhalation.
3. Taste and the smell of the medication can't be felt because the cloud of vapour is so fine.
4. As the drug particles is in fine form, they are carried deep into the lung

The technique for metered dose inhaler (MDI) use is as follows:

- The cap to be taken off and the inhaler to be held upright.
- The inhaler to be shaken before use.
- The head to be tilted back slightly and patient asked to breathe slowly and completely for 3-5 seconds.

- The individual is instructed to inhale in slowly and simultaneously the inhaler is pressed down for one time for releasing the medication; if there is valved holding chamber, inhaler to be press down first and then patient asked to inhale in slowly within five seconds.
- The individual asked to inhale in slowly, as uniformly and deeply .
- Breath is to be held if possible for upto ten to fifteen seconds ; to help the medications to reach deeply into the peripheral airways.
- The above procedure is to be repeated if more than 1 puff (actuation) is needed.
- A gap of one minute to be kept between each puff ; to improve penetration of next puff into peripheral airways.

Advantage of metered- dose inhaler with spacer over nebuliser [16]

1. portability, multidose delivery capability.
2. less requirement of maintenance, purchasing & power requirement.
3. lower bacterial contamination & cross infection.
4. enhanced efficiency of drug delivery, shorter delivery time &improvement in symptoms.

5. reduced oral absorption&lack of need for assistance Metered-dose inhalers (MDIs) and spacers are equally good as Nebulizers.

Advantages of nebulizers

Nebulizers have their ability to deliver larger dosages at a quicker rate, in patients with acute asthma .

Recent data shows that in both modes of delivery the lung deposition rates are the same. In addition, another trial found that a MDI (with spacer) - required lower dose for clinical improvement compared to a nebulizer .

Side effects of $Beta_2$ agonists-muscle tremor, tachycardia, hypokalemia, impaired glucose tolerance, decreased oxidation of fatty acids, decreased magnesium, lactic acidosis and relaxation of uterus.

Combined inhalation therapy with b2 agonists and oxygen are safe even when huge amount of doses are used.

SALBUTAMOL- MODE OF DELIVERY

NEBULIZER VERUS MDI-SPACER

Dhuper S et al conducted a study on 60 adult acute asthma patients (29-Spacer and 29-nebulizer).They emphasised that beta agonist delivery with a MDI/disposable spacer combination is an effective and low-cost alternative to nebulizer delivery for acute asthma[27].Hendeles L et al demonstrated that higher doses of albuterol delivered by MDI+VHC (4-10

puffs per dose) are as effective as 2.5 mg of albuterol sulfate delivered by SVN. They also conclude that MDI+VHC offers practical advantages over SVN, including the capacity for home use by the patient, portability, less setup time, and lack of need for daily disinfection[28]. Cavkaytar O et al showed that asthma exacerbation treated with pMDIs used through holding chambers in emergency room was successful compared to ordinary method of nebulizers[29].

Lombardi DM et al compared 90 patients with acute asthma treated with MDIs in December 2003 with a similar number treated with wet nebulizers in December 2002. Treatment with MDIs resulted in significant reduction in length of stay in the emergency department and an increase in the number of discharges in the first 2 hours of treatment. Patients in the MDI group received 87% of the scheduled bronchodilator doses, while patients in the wet nebulizer group received only 37% of the prescribed doses. Patients treated with bronchodilators delivered by MDI improved faster and had better fulfillment of treatment standards[30].

Colacone et al study concluded that the beneficial effect of salbutamol by MDI and spacer is similar to that by nebulizer in patients with acute severe asthma[31].

Theophylline

It produces broncho dilation by inhibiting phosphodiesterase and has a narrow therapeutic window. It can be used in acute severe asthma rather than chronic asthma.

Anti cholinergics

Anticholinergic agents are the better drugs for older patients compared to younger patients. These are usually used for the non responders to the regular doses of inhaled steroids in patients with chronic asthma. Its therapeutic role in acute severe asthma is of greater value than regular role in chronic asthma.

Anti-inflammatory drugs

Corticosteroids, mast cell stabilizers, Leukotriene antagonists

Corticosteroids - At present the first line of medication in the management of chronic asthma is Inhaled glucocorticosteroids. They have advantageous effects on the inflammation of walls of bronchioles and hyper-responsiveness of the airways as well as on clinical features. Budesonide is an inhaled corticosteroid with a higher local activity than systemic effects. It can reduce the chronic inflammatory process of asthma seen in patients with uncontrolled asthma.

Budesonide 200 microgram once daily is used in mild asthma by inhalation. High-dose inhaled corticosteroid is used in patients with increased severity of disease.

Side-effects-*Oropharyngeal candidiasis, Dysphonia, Cough and throat irritation,* increase in infections and systemic side-effects.

Mast cell stabilizers (cromolyn sodium, nedocromil)-act on mast cells preventing release of histamine by blocking calcium channels. It is useful in intermittent, mild asthma and as a prophylaxis in exercise and allergic asthma.

Leukotriene inhibitors act by blocking 5-lipoxygenase activity. It may be used in combination with inhaled corticosteroids as an add on therapy in the treatment of moderate persistent asthma. It is also effective in aspirin-induced asthma.

Immunotherapy

Specific allergy immunotherapy (desensitisation) is the technique for treating Ig E- mediated disease, with increasing doses of an allergen used in order to decrease the sensitivity to that allergen. Its usefulness in asthma is controversial.

Anti-Immunoglobulin E Ab (Omalizumab)- It acts by reducing circulating levels of IgE .It is useful in reducing exacerbations in asthma and in reducing the requirement of corticosteroids.

Protocol of step-up approach in chronic adult asthma

				Oral steroids
		Long acting beta 2 agonist	Long acting beta 2 agonist	Long acting beta 2 agonist
	inhaled low dose steroids	Inhaled low dose steroids	Inhaled high dose steroids	Inhaled high dose steroids
Short acting Beta 2 agonist	Short acting beta 2 agonist	Short acting beta 2 agonist	Short acting beta 2 agonist	Short acting beta 2 agonist
Mild intermittent	Mild Persistent	Moderate persistent	Severe persistent	Very severe persistent
STEP-1	STEP-2	STEP-3	STEP-4	STEP-5

AIMS AND OBJECTIVES

To analyse the efficacy of salbutamol administered by a nebuliser compared to metered- dose inhaler and spacer in adults with acute Asthma.

MATERIALS AND METHODS

The study was conducted on 52 patients admitted in the Medical ward of Government Rajaji Hospital, Madurai. Approval from the hospital ethical committee was obtained.

STUDY DESIGN:

The study was a cohort study conducted for a period of 6 months from May 2012 to October 2012.

Inclusion criteria:

In-patients of medical ward in GRH who have clinical features suggestive of bronchial asthma above 13 years of age were prospectively enrolled after informed consent.

The diagnosis was based on Pulmonary function tests showing decrease in expiratory flow rates :

- Reduction in forced expiratory volume over 1 sec (FEV_1) and a proportionally smaller reduction in the forced vital capacity (FVC) and decreased FEV_1/FVC ratio (generally <0.70) and reduction in PEFR with diurnal variability of Peak Expiratory Flow Rate > 20
- Reversibility test as determined by increase in Peak Expiratory Flow Rate (PEFR) more than twenty percent ; and more than twelve percent or 200-mL increase in Forced Expiratory Volume in 1 $second_1$15 minutes after an inhaled short-acting $Beta_2$-agonist.

Exclusion criteria:

1. Patients <13 yrs age.
2. Patients with acute respiratory tract infections, COPD and restrictive lung disease.
3. Patients with heart failure, renal failure and hepatic failure

Blood samples were collected for estimation of Blood urea, Serum creatinine and Liver function tests. ECG, ECHO,X RAY CHEST PA view were taken.

Methods:

Fifty two patients with acute asthma in the medical ward of Government Rajaji Hospital Madurai were enrolled in the study. All the fifty two patients in the study fulfilled the criteria of American Thoracic Society. Patients above the age of thirteen years with Peak Expiratory flow rates, Forced Expiratory Volume in 1 second below fifty percent of predicted value were eligible for the study. All the patients were on regular treatment with bronchodilators and steroids.

All fifty two patients in the study received bronchodilator- short acting Beta 2 agonist, salbutamol. The patients were divided into two groups depending on mode of delivery of salbutamol. The first group received salbutamol by nebuliser and the second group by metered dose inhaler and spacer. The twenty six patients in the first group received 0.5ml of

salbutamol (2.5mg) in 2.5 ml of NS via nebuliser. A face mask was used. The time of nebulisation was nearly 5 minutes and nebulisation was stopped when no suspension was found in the container .The patients in the second group received salbutamol via metered dose inhaler into a spacer in puffs sprayed one at a time at 5 minutes interval(one hundred micro gram per puff). The patients were instructed to inhale deeply from the spacer following each puff. The drug was administered in a double blinded manner. The drug dosage was increased in both the groups depending upon the patients' clinical improvement.

The following values were calculated before medication , after thirty minutes of drug delivery, and at the end of the treatment.

The variables were PEFR. FEV1, FVC, heart rate, respiratory rate, oxygen saturation and drug dosage. The PEFR was measured with a mini-wright peak flow meter. The highest of three values were recorded. FVC and FEV1 were measured using spirometer. Curves of expiration were recorded at each time and the maximum value was selected. This was done in 3 successive manners according to the American Thoracic society guidelines. Oxygen saturation was calculated using pulse oximeter. Drug dosage, heart rate and respiratory rate were also measured.

RESULTS

Table – 1

Age Distribution

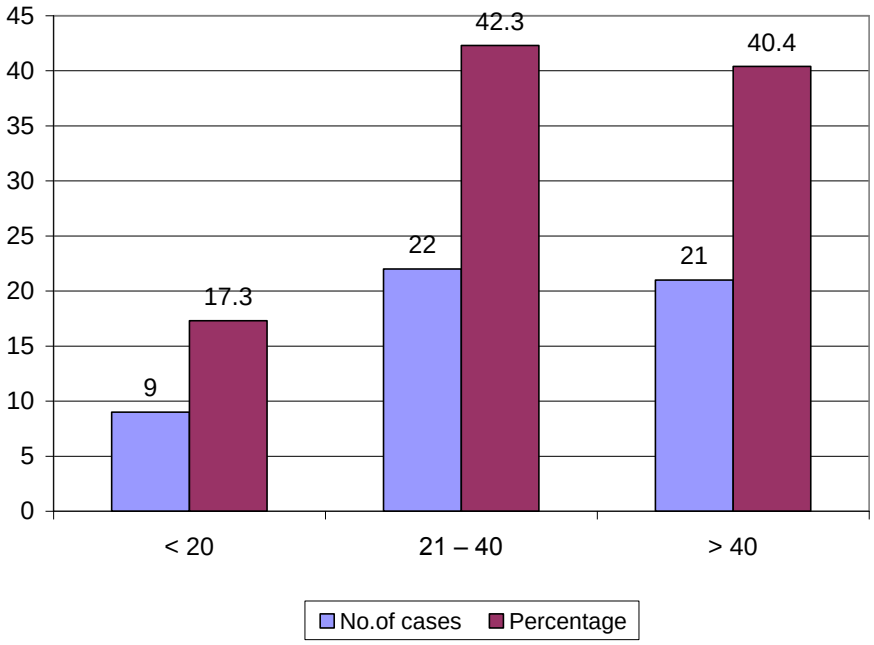
Age in years	No.of cases	Percentage
< 20	9	17.3
21 – 40	22	42.3
> 40	21	40.4
Total	52	100

Table – 2

Sex Distribution

Sex	No.of cases	Percentage
Male	33	63.4
Female	19	36.6
Total	52	100

AGE DISTRIBUTION



SEX DISTRIBUTION

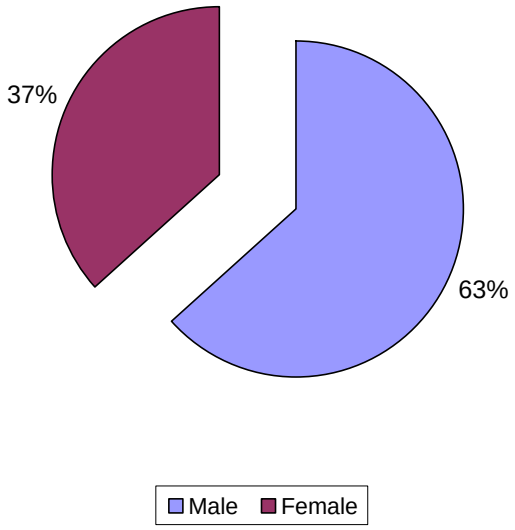


Table – 3

Duration of illness

Duration	No.of cases	Percentage
< 10 yrs	10	19.2
11 – 20 yrs	26	50.0
21 – 30 yrs	13	25.0
> 30 yrs	3	5.8
Total	52	100

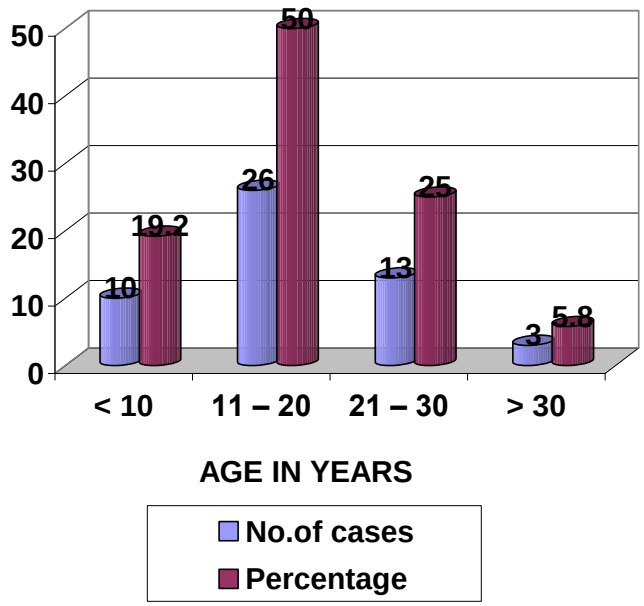
Table – 4

Seasonal Variation*

Season	No.of cases	Percentage
Yes	39	75
No	13	25
Total	52	100

*Asthmatic Symptoms occurs predominantly in winter

DURATION OF ILLNESS



SEASONAL VARIATION

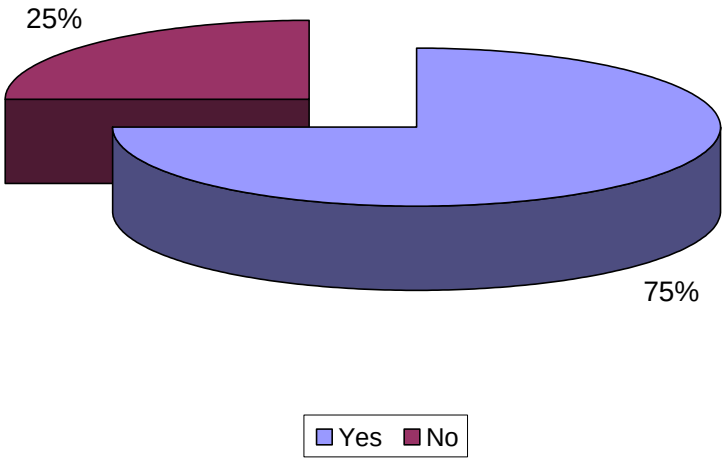


Table – 5

Diurnal Variation*

Diurinal	No.of cases	Percentage
Yes	40	76.9
No	12	23.1
Total	52	100

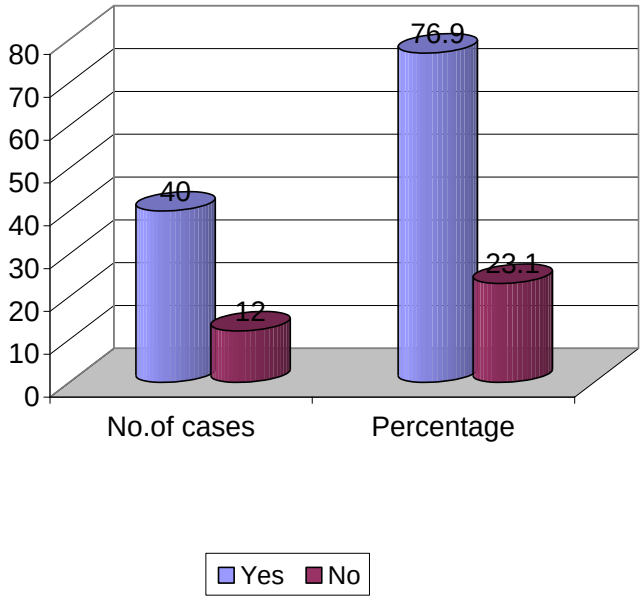
*Asthmatic symptoms occurs predominantly at night and early morning hours.

Table – 6

History of Allergy

Allergy	No.of cases	Percentage
Yes	42	80.8
No	10	19.2
Total	52	100

DIURNAL VARIATION



HISTORY OF ALLERGY

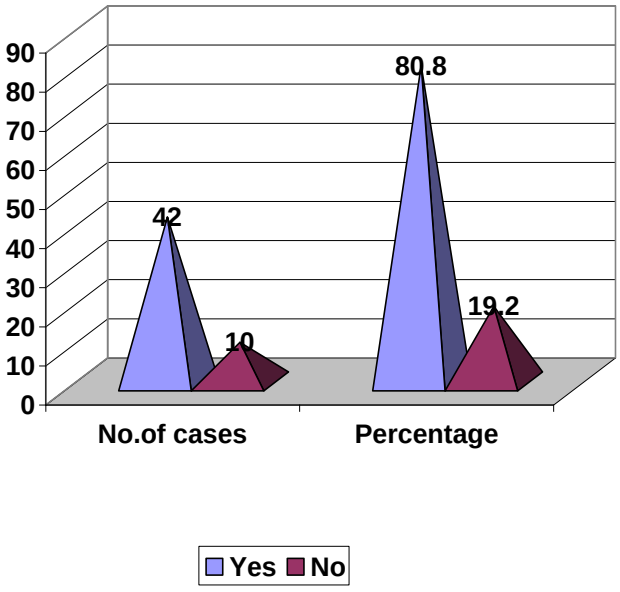


Table – 7

Family History

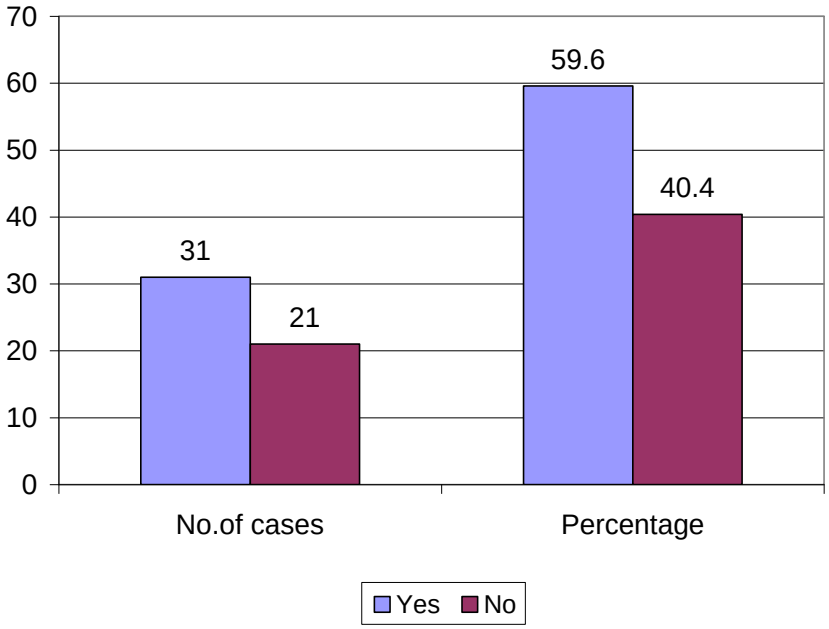
Family	No.of cases	Percentage
Yes	31	59.6
No	21	40.4
Total	52	100

Table – 8

Smoking History

Smoking	No.of cases	Percentage
Yes	14	26.9
No	38	73.1
Total	52	100

FAMILY HISTORY



SMOKING HISTORY

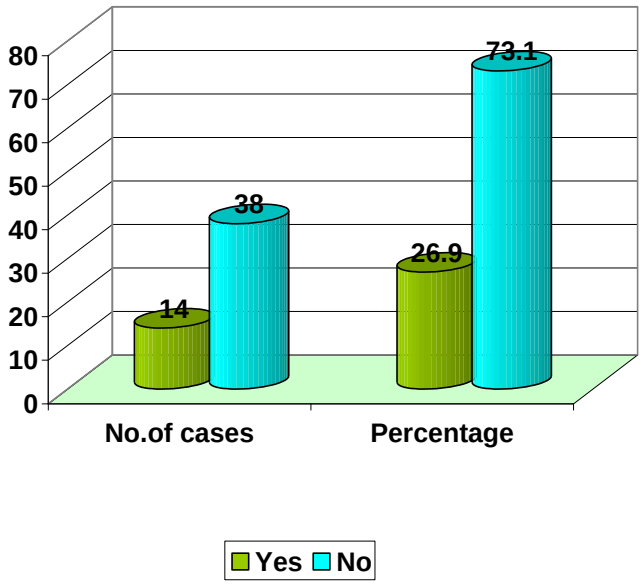


Table – 9

Frequency of Illness

Frequency	No.of cases	Percentage
Daily	20	38.5
< 2 /week	11	21.1
> 2/ week	21	40.4
Total	52	100

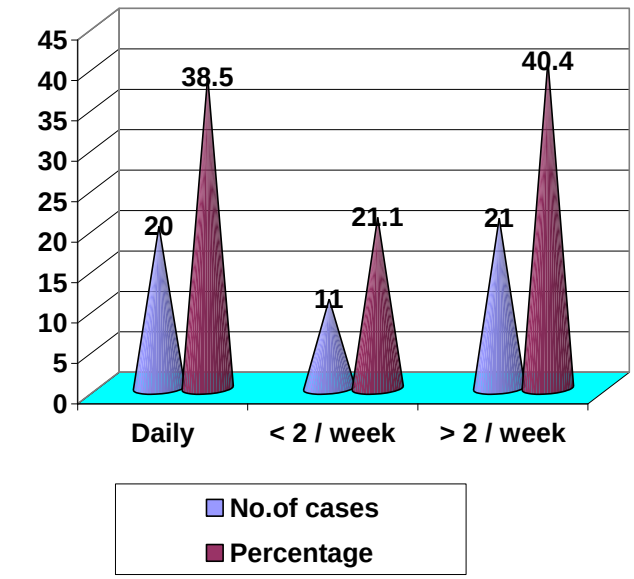
Table – 10

Salbutamol Mode of Delivery

MDI-S Vs Nebulizer

Salbutamol MOD	No.of cases	Percentage
MDI – S	26	50
Nebulizer	26	50
Total	52	100

FREQUENCY OF ILLNESS



SAL BUTAMOL MODE OF DELIVERY
NEBULISER VERSUS MDI-SPACER

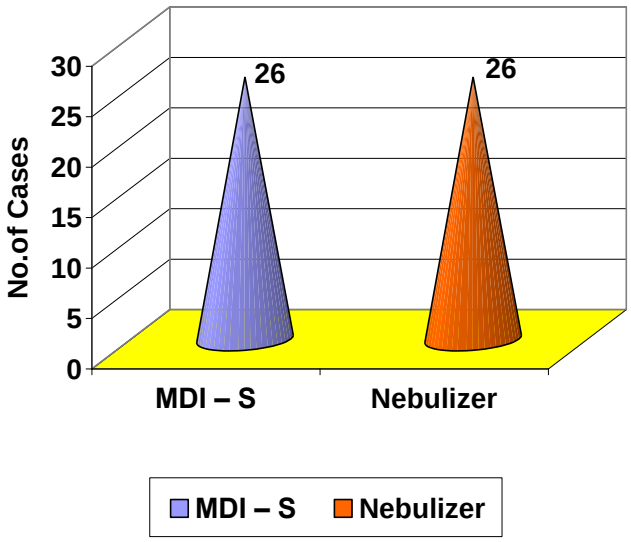


Table – 11

Change in PEFR-MDI -Spacer Vs Nebuliser(30 mts)

PEFR (30 min)	Mean	SD
MDI – Spacer (26)	212.31	7.65
Nebulizer (26)	189.62	9.16
'p' value	< 0.001 Significant	

Change in PEFR-MDI -Spacer Vs Nebuliser(end)

PEFR (end)	Mean	SD
MDI – Spacer (26)	227.31	10.02
Nebulizer (26)	210.77	9.77
'p' value	< 0.001 Significant	

There is stastistically significant improvement in PEFR at 30 mts and at end of treatment with the MDI-Spacer group than with the nebulised group.

Change in PEFR-MDI -Spacer Vs Nebuliser

(30 mts vs End)

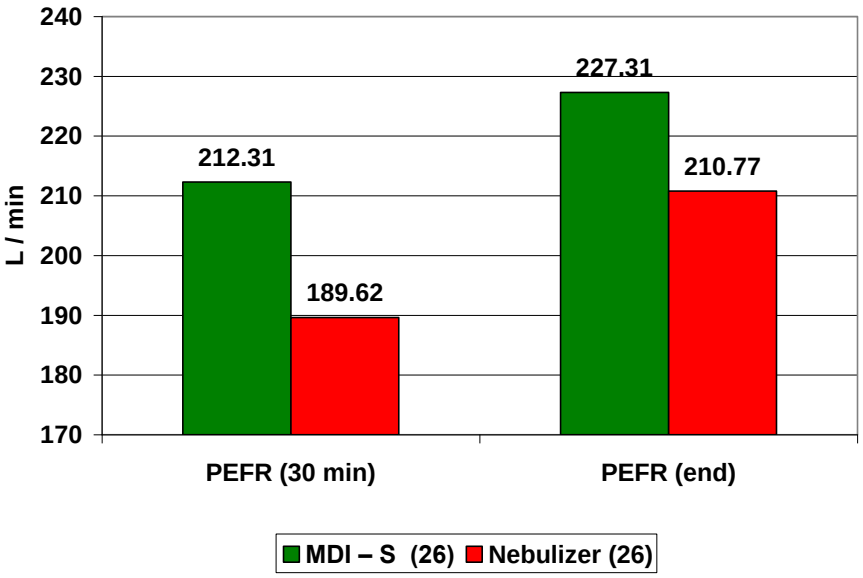


Table – 12

Change in FEV_1-MDI -Spacer Vs Nebuliser(30 mts)

FEV_1 (30 min)	Mean	SD
MDI – Spacer (26)	1.408	0.011
Nebulizer (26)	1.371	0.023
'p' value	< 0.001 Significant	

Change in FEV_1-MDI -Spacer Vs Nebuliser (end)

FEV_1 (end)	Mean	SD
MDI – Spacer (26)	1.635	0.028
Nebulizer (26)	1.602	0.015
'p' value	< 0.001 Significant	

There is stastistically significant improvement in FEV_1 at 30 mts and at end of treatment with the MDI-Spacer group than with the nebulised group.

Change in FEV_1-MDI -Spacer Vs Nebuliser

(30 mts vs End)

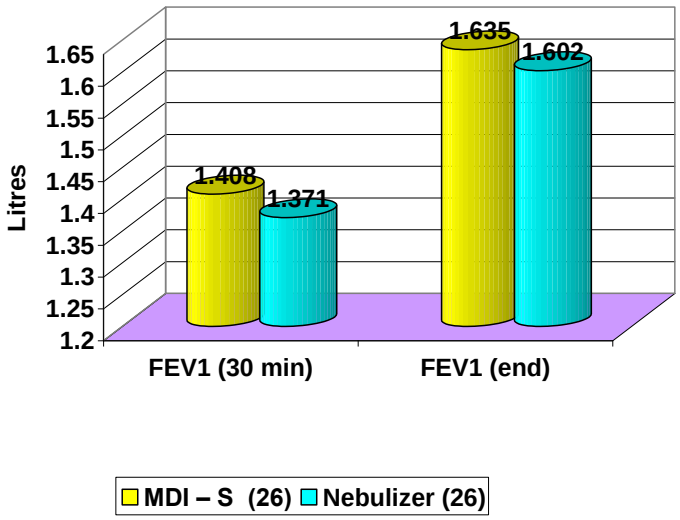


Table – 13

Change in FVC-MDI -Spacer Vs Nebuliser (30 mts)

FVC (30 min)	Mean	SD
MDI – Spacer (26)	1.425	0.025
Nebulizer (26)	1.396	0.020
'p' value	< 0.001 Significant	

Change in FVC-MDI -Spacer Vs Nebuliser (end)

FVC (end)	Mean	SD
MDI – Spacer (26)	1.656	0.022
Nebulizer (26)	1.622	0.013
'p' value	< 0.001 Significant	

There is stastistically significant improvement in FVC at 30 mts and at end of treatment with the MDI-Spacer group than with the nebulised group.

Change in FVC-MDI -Spacer Vs Nebuliser

(30 mts vs End)

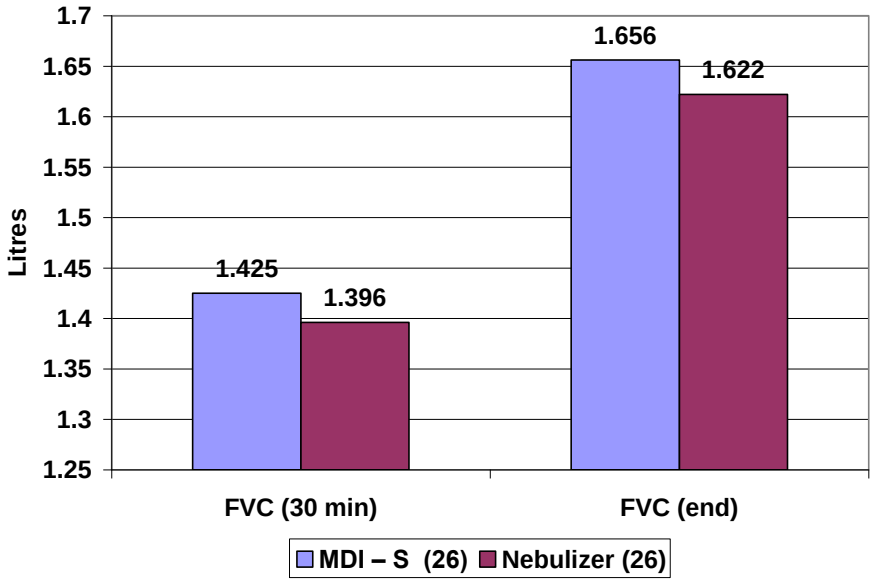


Table – 14

Change in SPO_2-MDI -Spacer Vs Nebuliser (30 mts)

SPO2 (30 min)	Mean	SD
MDI – Spacer (26)	3.92	0.404
Nebulizer (26)	2.23	0.430
'p' value	< 0.001 Significant	

Change in SPO_2-MDI -Spacer Vs Nebuliser (end)

SPO2 (end)	Mean	SD
MDI – Spacer (26)	2.23	0.430
Nebulizer (26)	2.12	0.326
'p' value	0.304 Not Significant	

There is statistically significant improvement in oxygen saturation at 30minutes in the MDI-spacer than in the nebuliser group but there is no significant difference at the end of treatment.

Change in SPO_2-MDI -Spacer Vs Nebuliser

(30 mts vs End)

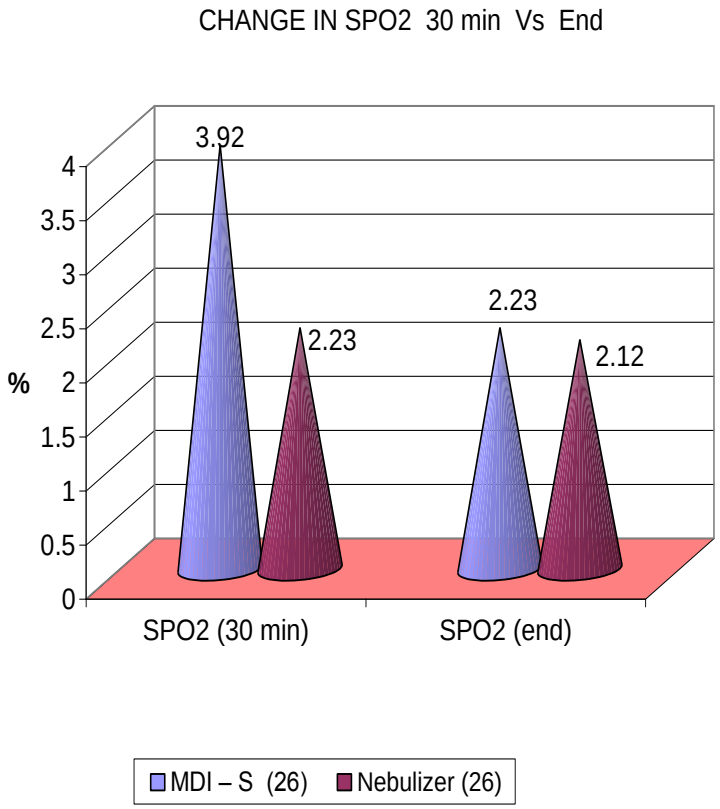


Table – 15

Change in Heart Rate -MDI-Spacer Versus Nebuliser (30 mts)

Heart Rate (30 min)	Mean	SD
MDI – S (26)	15.00	0.632
Nebulizer (26)	14.923	0.688
'p' value	0.677 Not Significant	

Change in Heart Rate -MDI-Spacer Versus Nebuliser (end)

Heart Rate (end)	Mean	SD
MDI – S (26)	9.923	0.272
Nebulizer (26)	9.423	1.391
'p' value	0.078 Not Significant	

There is no statistically significant difference between MDI-spacer and nebuliser groups in the heart rate at 30 minutes and at the end of treatment.

Change in Heart Rate -MDI-Spacer Versus Nebuliser

(30 mts vs End)

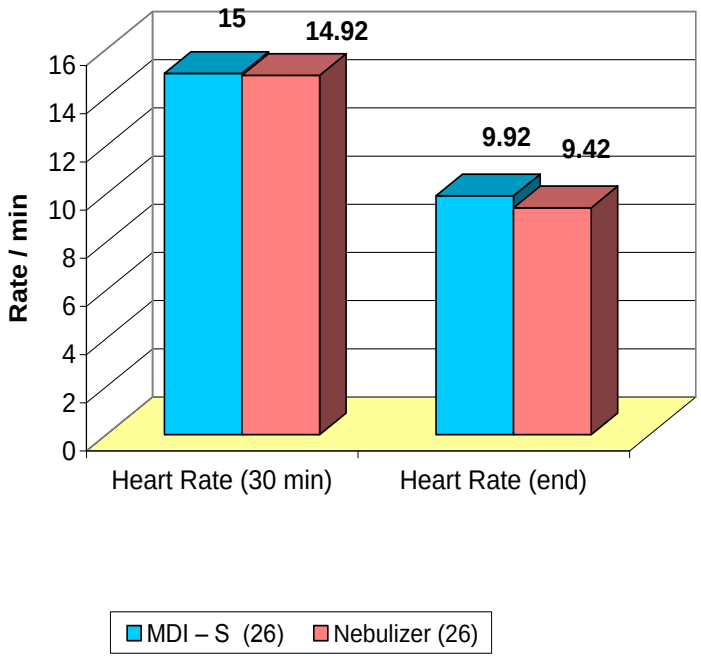


Table – 16

Change in Respiratory Rate-MDI-Spacer Versus Nebuliser (30 mts)

R R (30 min)	Mean	SD
MDI – S (26)	14.808	0.567
Nebulizer (26)	14.538	0.508
'p' value	0.077 Not Significant	

Change in Respiratory Rate-MDI-Spacer Versus Nebuliser (30 mts)

RR (end)	Mean	SD
MDI – S (26)	5.077	5.077
Nebulizer (26)	5.038	0.196
'p' value	0.561 Not Significant	

There is no statistically significant difference between MDI-spacer and nebuliser groups in the respiratory rate at 30 minutes and at the end of treatment.

Change in Respiratory Rate-MDI-Spacer Versus Nebuliser

(30 mts vs End)

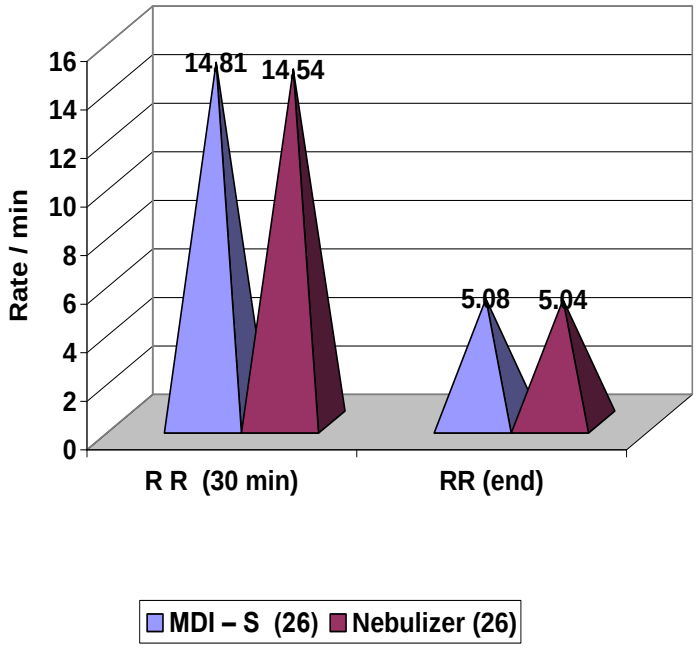
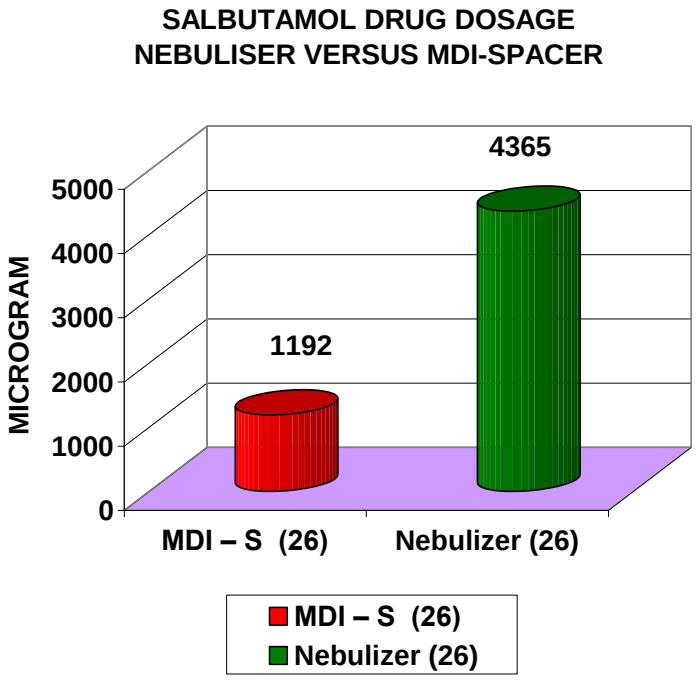


Table – 17

Total dosage of salbutamol-MDI-Spacer versus Nebuliser.

Drug Doses	Mean	SD
MDI – S (26)	1192.3	146.76
Nebulizer (26)	4365.3	1836.07
'p' value	< 0.001 Significant	

The requirement of salbutamol in MDI-spacer is significantly lower than nebulizer as suggested by p value less than .001.



RESULTS

A total of 52 patients with acute Bronchial asthma who received salbutamol therapy participated in the study. The patients were divided into 2 groups: 26 (50%) patients in the MDI-Spacer group and 26 (50%) patients in the Nebuliser group. The baseline characteristics of over all cohort were expressed in percentage. Age distribution was 17.3%(<20yrs),42.3%(21-40yrs), 40.4%(>40yrs) as shown in Table 1.Sex distribution was males (63.4%) and females(36.6%)as shown in Table 2.Duration of illness was 19.2%(10yrs),50%(11-20yrs),25%(21-30yrs) and 5.8%(>30yrs) as shown in Table 3.Table 4. shows 75% of patients with seasonal variation and 25% with no seasonal variation. Diurnal variation was demonstrated in76.9% of patients but not in the rest 23.1% ,as illustrated in Table 5.As per Table 6,a positive history of allergy is seen in 80.8% and is negative in 19.2%. As shown in Table 7, 59.6% of patients have a positive family history and 40.4% do not. 26.9% of patients had a history of smoking and 73.1% were non smokers(Table 8). The frequency of illness was 38.5%(daily),21.1%(<2/week) and 40.4%(>2/ week) as depicted in Table 9.

The two treatment groups were comparable as regards change in PEFR, FEV_1, FVC, Oxygen saturation, heart rate, respiratory rate and drug dosage at thirty minutes and at the end of treatment. Mean PEFR,FEV_1,FVC and oxygen saturation values improved significantly over

base line values in both nebuliser and MDI-spacer groups. They were expressed as mean and standard deviation. The magnitude of improvement in PEFR at 30 minutes were 212.31 ±7.65 in the MDI-Spacer group and 189.62±9.16 in the nebulised group and at the end of treatment 227.31±10.02 in the MDI-spacer group and 210.77±9.77 in the nebulised group(table-11).PEFR has statistically significant difference ($p < 0.001$) in MDI-spacer than nebulised group at 30 mts and at the end of treatment. Change in FEV_1 in the MDI-spacer group and nebulised group at 30 minutes were 1.408±0.011 and 1.371±0.023 and at the end of treatment were 1.635±0.028 and 1.602±0.015 respectively(table-12). FEV_1 has statistically significant difference ($p < 0.001$) in MDI-spacer than nebulised group at 30 mts and at the end of treatment. The same pattern was held for change in FVC in the MDI-spacer group and nebulised group;the values at 30 minutes were 1.425±0.025 and 1.396±0.020 and at the end of treatment were 1.656±0.022 and 1.622± 0.013 respectively(table-13). FVC has statistically significant difference ($p < 0.001$) in MDI-spacer than nebulised group at 30 mts and at the end of treatment. Change in oxygen saturation at 30mts was 3.92±0.404 (MDI-Spacer) and 2.23±0.430 (nebulised group) .It was significant with $p<0.001$ at 30mts.At the end of treatment the corresponding values were 2.23±0.430(MDI-spacer) and 2.12± .33)(nebulised group)Table 14.There was no statistically significant

difference (p 0.304). The change in heart rate at 30 mts and at the end of treatment were 15±0.63 and 9.92±0.27 in the spacer group and 14.92±0.69 and 9.42±1.40 in the nebulised group respectively(p 0.677)(table-15), Change in Respiratory rate at 30 mts and at the end of treatment were14.81±0.57 and 5.07±5.07 in the spacer group and 14.54±0.51and 5.04±0.19 in the nebulised group .p values were 0.07(30mts) and 0.5619(end of treatment)(table-16). Heart rate and respiratory rate changes were not significantly affected by the mode of delivery. Drug dosage in the MDI group was 1192.3±146.76 and 4365.3±1836.07 in the nebulised group, it was statistically significant,with $p<0.001$.(table-17)

Statistical analysis:

Analysis was performed with SIGMA STAT VERSION 3.5 statistical package. All continuous variables were presented as mean ±standard deviation if they were normally distributed. One way Anova Analysis and Chi square test was performed to study the comparison between nebuliser and MDI -spacer. Differences in the normally distributed variables were assessed using *t*-test and paired *t*-test for dependent variables. Comparisons between the two individual groups were performed using the unpaired *t*-test (parametric) All tests were two-sided and a probability value of $p < 0.05$ was considered as significant.

DISCUSSION

Patients with Acute asthma arrive at our hospital relatively rapidly due to its central location and most of the patients could obtain maximum and rapid benefit by bronchodilators provided by government free of cost. Several modes of therapy for acute exacerbation of asthma have been developed which differ in terms of effectiveness, complexity and cost. Currently, the most relevant treatment options are: Bronchodilators(short acting beta 2 agonist) (salbutamol, terbutaline, fenoterol), Anticholinergics and Corticosteroids.

Short acting beta 2 agonist is the treatment option which quickly relieves bronchospasm .Reversibility with bronchodilators predicts a good outcome in acute bronchial asthma. It can be delivered by Nebuliser and MDI with spacer. Now-a-days MDI and spacer is useful in acute asthma. The clinical significance of MDI and spacer lies is the amount of drug that reaches lower airways. It depends upon the aerodynamic mass median diameter. According to Mazhar SH et al study[26], in nebuliser only ten percent of the dose reaches the lungs after leaving the nebuliser. In contrast, in MDI with spacer approximately twenty percent of drug dosage is deposited in the peripheral airways. Spacers are known to improve the compliance of the patient, increase the efficacy of drug delivery and reduce oral absorption compared to MDI without spacers or holding chamber. Their

use is particularly valuable in patients who have poor timing and do not adequately coordinate inhalation from an MDI with the actuation of the device. MDI requires less drug dosage compared to a nebuliser.

Kenneth B. Newman *et al* [22]who reported there was a statistically greater improvement in peak flow rates in the MDI/spacer group vs nebulized group (126.8 vs 111.9 L/minute, respectively; p value equal to .002), had showed a lesser total salbutamol dosage (one thousand and hundred twenty five micro gm and six thousand and seven hundred micro. gm, respectively; p value less than 0.001), and showed a maximum improvement in Sa O_2 (p value equal to 0.043).According to RODRIGO et al [23] study there was a significant improvement in PEFR, $FEV_{1,}$FVC at 30 mts and at the end of treatment in MDI spacer group compared to nebulised group. The magnitude of improvement of PEFR at 30 minutes was (77+/-46Litre/minute) in the nebuliser category and (83+/-61 Litre/minute) in the Metered Dose Inhaler-spacer category ; (p value less than .01)and at the end of therapeutic trial(112+/-52Litre/minute in the nebuliser category and 119 Litre /minute) in the Metered Dose Inhaler –spacer category ;(p value less than 0.001) .The improvement of average Forced Vital Capacity was significant over pretreatment values in both nebuliser and Metered Dose Inhaler-spacer categories;(p value less than .001);the values at thirty mts being (.7+/- .4 Litres and .7+/-.6 Litres), respectively for nebulised and

MDI spacer; (p value less than .01) and (1+/- .6Litres and 1.0+/-0 .7 Litres,) respectively; (p value less than .001) after the cessation of therapy. Similar changes in measurements was held for FEV_1. At thirty minutes, FEV_1 increased by (0.5+/-0.3Litres) in nebuliser category and (0.6+/-0.5 Litres) in Metered Dose Inhaler-spacer category (p value less than .01). At the end of therapeutic trial Forced Expiratory Volume in 1 second increased (.8 +/- .4 Litres) in nebuliser category and (.9 +/- .5 Litres) in Metered Dose Inhaler-spacer category (p value less than .001) But there was no statistically significant difference in heart rate between the nebulised and Metered Dose Inhaler-Spacer group. Dosage of salbutamol in Metered Dose Inhaler group was lower compared to nebulised group.

Idris et al[25] reported that a significant improvement occurs in average Forced Expiratory Volume in 1second at thirty minutes (p value less than .02) and at sixty minutes (p value less than .02) and in maximum average (p value is less than .001).

According to Christopher J Cates[24], statistically significant differences were seen between the two categories in baseline pulmonary function. Results were presented only as change in Pulmonary function from the baseline, and this favoured the spacer. There were no significant differences demonstrated between the two categories in their outcomes : change in respiratory rate and oxygen saturation.

Limitations

Some patients did not respond to short acting beta2 agonists even after maximum doses were given, they were switched over to systemic medications like corticosteroids. Others were not able to perform pulmonary function tests before the medication because of poor compliance. Patients presenting with Status asthmaticus and Near fatal asthma required life saving measures apart from routine medications. Reversibility with Bronchodilators did not occur with a few patients, who had associated chronic obstructive pulmonary disease or had developed chronic inflammatory process in asthma leading to irreversible air flow obstruction. These patients were not included in the study.

CONCLUSION

1. Base line characters were not comparable in the study. The patients were equally divided into two groups for better comparison.
2. PEFR improvement was significant at 30 mts and at end of treatment with the MDI-Spacer group than the nebulised group.
3. FEV_1 improvement was also significant at 30 mts and at end of treatment with the MDI-Spacer group than the nebulised group.
4. FVC improvement was also significant at 30 mts and at end of treatment with the MDI-Spacer group than the nebulised group.
5. For oxygen saturation, the magnitude of improvement was significant at 30 mts in the spacer group, but at the end of treatment the improvements were similar in both the groups.
6. Heart rate and respiratory rate improvement was present in both groups and were similar in both at 30 mts and at the end of treatment.
7. Clinical improvement was achieved even at a lower dosage in the MDI-spacer group compared to nebuliser group.

Salbutamol administration by metered dose inhaler and spacer is as efficacious as nebuliser in adults with acute asthma. Now-a-days Metered Dose Inhaler and Spacer is the best alternative to nebuliser in acute asthma.

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CASE PROFORMA

Name: Sex:

Age: Occupation:

CLINICAL PROFILE:

Difficulty in breathing

Diurnal variation

Seasonal variation

Cough with expectoration

Total duration of illness: Frequency of illness:

Smoking history: Family history:

Allergic history: Treatment history:

System Examination:Level of consciousness Cyanosis

Able to speak in words Pulse rate Respiratory rate

Pulsus paradoxus Blood pressure JVP

Action of accessory muscle of respiration-

Examination of CVS- P/A-

RS- CNS-

INVESTIGATION:

Blood urea : Serum creatinine:

ECG: ECHO:

X RAY CHEST PA view:

Liver function test:

Serum total bilirubin- SGOT- SGPT-

S.Alkaline phosphate-

Pulmonary function test:

Administration of salbutamol:Nebuliser/Metered dose inhaler and spacer

PFT	0mts	30mts	End
1.PEFR			
2.FEV1			
3.FVC			
4.Oxygen saturation			
5.Drug dosage			
6.Pulse rate			
7.Respiratory rate			

ABBREVIATIONS

MDI-S	-	Metered Dose Inhaler and Spacer.
PEFR	-	Peak Expiratory Flow Rate.
FEV_1	-	Forced Expiratory Volume in One Second.
FVC	-	Forced Vital Capacity.
VHC	-	Valved Holding Chamber.
PFT	-	Pulmonary Function Test.
SVN	-	Small Volume Nebuliser.
COPD	-	Chronic Obstructive Pulmonary Disease.
ROI	-	Reactive Oxygen Intermediates.
IL	-	Interleukin.
Pa O2	-	Partial Pressure of Oxygen.
Pa CO_2	-	Partial Pressure of Carbon dioxide.
Sa O_2	-	Oxygen Saturation.

MASTER CHART

S.No.	Age (yr)	sex	duration (yr)	height (cm)	season	diurnal	allergy	family	smoking	Frequency	sal.mol	pre-med PEFR (L/mt)	post-med PEFR 30 mts	PEFR end	Change in PEFR 30 mts	change in PEFR end	PRE MED FEV1 (L)	post med FEV1 in 30 mt	FEV1 End	Change in FEV 1 in 30 mt	FEV1 end	pre med FVC (L)	post med FVC	FVC(L)	change in FVC in 30 mt	FVC end	pre med SPO2 (%)	Post med SPO2 30 mt	SPO2 end	Change in SPO2 30 mt	Change in SPO2 end	pre med HR / mt	Post med HR 30 mt	Post med HR end	change in HR 30 mt	change in HR end	pre med RR / mt	post med RR 30 mt	Post med RR end	change in RR 30 mt	Change in RR end	drug dosage in micro gm
1	40	M	20	170	yes	no	no	no	no	daily	MDI-S	280	480	500	200	220	0.87	2.25	2.53	1.38	1.66	1.3	2.7	3	1.40	1.68	93	97	99	4	2	140	126	116	14	10	40	25	20	15	5	1000
2	43	f	33	154	yes	yes	yes	no	no	daily	MDI-S	300	510	530	210	230	0.76	2.16	2.40	1.40	1.64	1.2	2.6	2.8	1.4	1.7	92	96	98	4	2	146	131	121	14	10	45	30	25	15	5	1200
3	35	f	18	160	no	yes	yes	yes	no	>2/wk	MDI-S	290	490	500	200	210	0.56	1.96	2.18	1.40	1.62	0.8	2.3	2.5	1.4	1.6	93	97	99	4	2	140	126	116	14	10	48	33	28	15	5	1000
4	32	f	15	165	yes	yes	yes	no	n0	>2/wk	neb	310	500	510	190	200	0.9	2.3	2.5	1.4	1.6	1.4	2.8	3	1.4	1.6	93	95	98	2	3	140	125	110	15	10	42	28	23	14	5	5000
5	30	m	5	160	no	yes	no	no	yes	<2/wk	neb	300	490	510	190	210	1	2.3	2.5	1.3	1.6	1.4	2.7	2.6	1.4	1.6	94	96	98	2	2	143	128	118	15	10	44	30	25	14	5	2500
6	60	m	15	170	yes	no	no	yes	no	daily	MDI-S	280	480	490	200	210	0.9	2.3	2.5	1.4	1.6	1.3	2.7	2.9	1.4	1.7	92	96	98	4	2	140	125	115	15	10	40	25	20	15	5	1100
7	55	m	25	160	no	yes	no	no	yes	daily	neb	290	490	500	200	210	0.8	2.2	2.4	1.4	1.6	1.2	2.6	2.8	1.4	1.6	93	96	99	3	3	142	128	117	14	11	44	29	24	15	5	5000
8	13	m	12	145	yes	yes	yes	yes	no	<2/wk	MDI-S	180	390	420	210	240	0.8	2.2	2.5	1.4	1.6	1.2	2.7	2.9	1.4	1.7	91	95	98	4	3	138	124	114	14	10	48	33	28	15	5	1200
9	17	m	12	150	yes	yes	yes	no	no	>2/wk	MDI-S	200	420	430	220	230	0.7	2.1	2.4	1.4	1.7	1.1	2.6	2.7	1.4	1.6	93	97	99	4	2	135	120	110	15	10	52	36	31	16	5	1300
10	20	f	5	155	yes	yes	no	yes	no	<2/wk	neb	200	380	440	180	240	0.8	2.2	2.4	1.4	1.6	1.2	2.6	2.8	1.4	1.6	94	96	98	2	2	140	125	115	15	10	44	29	24	15	5	5000
11	60	m	30	160	no	yes	yes	yes	yes	>2/wk	neb	250	450	470	200	220	1	2.4	2.6	1.4	1.6	1.4	2.8	3	1.4	1.6	93	96	98	3	2	130	115	105	15	10	40	26	21	14	5	2500
12	55	f	20	165	yes	yes	yes	no	no	daily	MDI-S	290	490	500	200	210	0.7	2.1	2.3	1.4	1.6	1	2.5	2.7	1.4	1.6	92	96	99	4	3	130	115	105	15	10	44	29	24	15	5	1200
13	56	f	>25	165	yes	no	yes	yes	no	daily	neb	300	490	520	190	220	0.9	2.3	2.5	1.4	1.6	1.3	2.7	2.9	1.4	1.6	92	94	96	2	2	146	132	122	14	10	48	34	29	14	5	5000
14	42	m	15	170	no	yes	yes	no	no	<2/wk	neb	310	490	540	180	230	1	2.4	2.6	1.4	1.6	1.5	2.8	3.1	1.4	1.6	93	96	98	3	2	140	124	114	16	10	40	25	20	15	5	2500
15	31	m	>25	165	yes	yes	yes	yes	yes	>2/wk	MDI-S	320	530	540	210	220	0.7	2.1	2.4	1.4	1.6	1.2	2.7	2.9	1.4	1.7	93	96	98	3	2	136	121	111	15	10	44	29	24	15	5	1100
16	23	m	>10	160	yes	yes	yes	yes	no	>2/wk	MDI-S	270	490	500	220	230	0.8	2.2	2.4	1.4	1.6	1.2	2.6	2.8	1.4	1.6	91	95	97	5	2	140	126	116	14	10	55	40	34	15	6	1200
17	46	m	>20	170	yes	no	yes	no	yes	daily	neb	330	410	440	180	210	0.6	2	2.2	1.4	1.6	0.9	2.3	2.5	1.4	1.6	92	94	96	2	2	140	125	116	15	9	44	30	25	14	5	5000
18	25	f	>20	150	yes	yes	yes	yes	no	>2/wk	MDI-S	250	470	490	220	240	0.6	2	2.3	1.4	1.6	1	2.4	2.7	1.4	1.7	93	97	99	4	2	135	125	115	15	10	50	35	30	15	5	1300

19	40	m	>20	170	no	yes	no	no	no	>2/wk	neb	300	510	520	210	220	0.7	2.1	2.2	1.4	1.6	1	2.5	2.6	1.4	1.6	95	97	99	2	2	138	124	114	14	10	46	31	26	15	5	7500
20	17	f	3	154	yes	yes	yes	yes	no	>2/wk	MDI-S	250	470	480	220	230	1	2.4	2.6	1.4	1.6	1.4	2.9	3.1	1.4	1.7	93	96	99	3	3	140	126	116	14	10	46	32	27	14	5	1000
21	53	f	>20	160	yes	no	yes	yes	no	daily	MDI-S	320	530	560	210	240	1	2.4	2.6	1.4	1.6	1.5	2.9	3.1	1.4	1.6	92	96	98	4	2	140	125 116	116	15	9	44	28	23	16	5	1000
22	53	m	>15	168	yes	no	yes	no	yes	daily	neb	290	480	500	190	210	0.9	2.3	2.5	1.4	1.6	1.4	2.8	3	1.4	1.6	95	97	99	2	2	134	119	110	15	9	38	23	17	15	6	2500
23	15	m	>12	150	yes	yes	yes	yes	no	>2/wk	MDI-S	250	470	480	220	230	0.9	2.4	2.6	1.4	1.7	1.4	2.8	3.1	1.4	1.7	93	97	99	4	2	136	121	111	15	10	40	25	20	15	5	1200
24	42	m	10	170	no	yes	yes	no	no	daily	neb	340	520	540	180	200	0.8	2.2	2.5	1.3	1.6	1.4	2.7	3	1.4	1.6	93	95	97	2	2	130	115	105	15	10	38	24	18	14	5	5000
25	31	m	>20	162	yes	yes	yes	yes	no	>2/wk	neb	380	580	590	200	210	1	2.4	2.6	1.4	1.6	1.6	2.9	3.2	1.4	1.6	92	94	96	2	2	135	124	114	14	10	38	23	18	15	5	2500
26	42	m	18	168	yes	yes	yes	no	yes	>2/wk	MDI-S	270	480	490	210	220	0.9	2.3	2.6	1.4	1.7	1.4	2.8	3.1	1.4	1.7	92	96	98	4	2	138	123	113	15	10	38	22	17	15	5	1100
27	40	f	15	150	no	yes	no	no	no	daily	MDI-S	310	520	540	210	230	0.8	2.2	2.4	1.4	1.6	1.3	2.7	2.9	1.4	1.7	93	97	99	4	2	140	124	114	16	10	48	33	28	15	5	1300
28	32	f	15	158	yes	no	yes	yes	no	daily	MDI-S	300	500	510	200	210	0.8	2.2	2.4	1.4	1.6	1.2	2.6	2.8	1.4	1.6	93	97	99	4	2	130	116	106	16	10	46	32	27	14	5	1200
29	38	f	10	167	no	yes	yes	yes	no	daily	neb	320	510	520	190	200	0.9	2.3	2.5	1.4	1.6	1.3	2.7	2.9	1.4	1.6	94	96	98	2	2	142	128	118	14	10	40	25	20	15	5	5000
30	32	m	8	162	yes	yes	yes	yes	no	>2/wk	neb	310	490	520	180	210	1	2.3	2.6	1.3	1.6	1.4	2.8	3	1.4	1.6	94	96	98	2	2	145	130	120	15	10	38	23	18	15	5	7500
31	58	m	18	168	yes	no	yes	yes	yes	<2/wk	MDI-S	290	500	510	210	220	0.9	2.3	2.5	1.4	1.6	1.3	2.7	3	1.4	1.7	93	97	99	4	2	142	128	118	14	10	40	25	5	15	5	1100
32	53	m	20	164	no	yes	yes	yes	no	>2/wk	neb	300	500	510	200	210	0.8	2.2	2.4	1.4	1.6	1.2	2.6	2.8	1.4	1.6	94	97	99	3	3	144	128	118	16	10	42	28	29	14	5	2500
33	16	m	13	150	yes	yes	yes	yes	no	>2/wk	MDI-S	200	410	440	210	240	0.9	2.3	2.5	1.4	1.6	1.2	2.7	2.9	1.4	1.7	92	96	99	4	3	132	117	108	15	9	46	31	26	15	5	1200
34	18	m	15	154	yes	yes	yes	yes	no	<2/wk	MDI-S	280	500	510	220	230	0.8	2.2	2.4	1.4	1.7	1.2	2.6	2.8	1.4	1.7	93	97	99	4	2	1	127	117	15	10	50	35	30	15	5	1000
35	25	f	10	153	yes	yes	no	no	no	>2/wk	neb	290	470	490	180	200	0.8	2.2	2.4	1.4	1.6	`1.12	2.5	2.8	1.4	1.6	94	96	98	2	2	144	129	119	15	10	42	27	22	15	5	5000
36	55	m	35	164	yes	no	yes	yes	yes	daily	neb	280	480	490	200	210	0.9	2.3	2.5	1.4	1.6	1.4	2.8	3	1.4	1.6	94	97	99	3	2	140	125	115	15	10	42	28	23	14	5	7500
37	52	f	30	163	no	yes	no	no	no	daily	MDI-S	300	510	520	210	220	0.9	2.3	2.4	1.4	1.5	1.3	2.6	3	1.4	1.6	92	96	99	4	3	130	116	106	14	10	46	31	26	15	5	1400
38	48	f	20	160	yes	yes	yes	yes	no	>2/wk	neb	310	500	530	190	220	0.8	2.2	2.4	1.4	1.6	1.2	2.6	2.8	1.4	1.6	94	96	98	2	2	140	124	115	16	9	46	32	27	14	5	2500
39	38	m	10	168	yes	yes	yes	no	yes	>2/wk	neb	320	500	520	180	200	1	2.3	2.6	1.4	1.6	1.4	2.7	3	1.4	1.6	94	97	99	3	2	142	127	118	15	9	38	23	18	15	5	5000
40	28	m	20	163	yes	yes	yes	yes	no	<2/wk	MDI-S	330	550	560	220	230	0.8	2.2	2.4	1.4	1.6	1.2	2.5	2.8	1.3	1.7	94	97	99	3	2	138	123	113	15	10	46	32	27	14	5	1400
41	25	m	15	163	yes	yes	yes	yes	no	<2/wk	MDI-S	290	510	520	220	230	0.8	2.3	2.5	1.4	1.6	1.2	2.7	2.9	1.4	1.6	92	97	99	5	2	140	124	114	16	10	45	30	25	15	5	1500

42	43	m	18	168	yes	no	yes	yes	no	daily	neb	340	520	550	180	210	0.8	2.2	2.4	1.4	1.6	1.2	2.6	2.8	1.4	1.6	93	95	97	2	2	145	130	121	15	9	40	25	20	15	5	2500
43	28	f	20	154	yes	yes	yes	yes	no	<2/wk	MDI-S	300	520	540	220	240	0.8	2.2	2.5	1.4	1.6	1.2	2.6	2.9	1.4	1.7	92	96	98	4	2	140	126	116	14	10	45	30	25	15	5	1300
44	43	m	25	166	no	yes	no	no	yes	daily	neb	300	500	510	200	210	0.9	2.3	2.4	1.4	1.6	1.2	2.7	2.8	1.4	1.6	94	96	98	2	2	138	124	114	14	10	48	34	33	14	5	2500
45	15	f	5	150	yes	yes	yes	yes	no	<2/wk	MDI-S	290	510	520	220	230	0.9	2.4	2.6	1.4	1.6	1.4	2.9	3.1	1.4	1.7	92	95	98	3	3	1	119	109	16	10	44	30	25	14	5	1000
46	50	f	>30	164	yes	no	yes	yes	no	daily	MDI-S	320	530	560	210	240	1	2.4	2.6	1.4	1.6	1.5	2.9	3.1	1.4	1.6	93	97	99	4	2	145	130	120	15	10	46	30	25	16	5	1300
47	56	m	>20	166	no	yes	yes	no	yes	daily	neb	300	490	510	190	210	0.9	2.3	2.5	1.4	1.6	1.4	2.8	3	1.4	1.6	94	96	98	2	2	148	134	125	14	9	40	26	20	14	6	6000
48	17	m	>15	154	yes	yes	yes	yes	no	>2/wk	MDI-S	280	500	510	220	230	0.9	2.3	2.6	1.4	1.7	1.3	2.8	3	1.4	1.7	93	97	99	4	2	130	115	105	15	10	38	23	18	15	5	1400
49	40	m	>15	168	yes	no	yes	no	yes	daily	neb	340	520	540	180	200	0.9	2.2	2.5	1.4	1.6	1.3	2.7	2.9	1.4	1.6	94	96	98	2	2	140	125	115	15	10	40	25	20	15	5	2500
50	30	m	>20	160	yes	yes	yes	yes	no	>2/wk	neb	380	580	590	200	210	1	2.3	2.5	1.4	1.6	1.4	2.8	3	1.4	1.6	95	97	99	2	2	148	130	126	16	10	40	26	21	14	5	2500
51	37	f	10	154	yes	yes	yes	no	no	<2/wk	neb	360	540	560	180	200	0.9	2.3	2.5	1.4	1.6	1.3	2.8	3	1.4	1.6	93	95	97	2	2	143	128	123	15	5	44	29	25	15	5	7500
52	30	m	20	160	yes	yes	yes	yes	yes	>2/wk	neb	320	510	530	190	210	0.9	2.3	2.5	1.4	1.6	1.4	2.8	3	1.4	1.6	94	96	98	2	2	138	122	117	16	5	48	33	27	15	5	5000

Depart. Medicine

Ref. No. 5336 /E4/3/2012 Govt. Rajaji Hospital,
Madurai.20. Dated: .08.2012

Institutional Review Board / Independent Ethics Committee.

Dr. N. Mohan, M.S., F.I.C.S., F.A.I.S.,
Dean, Madurai Medical College & 2521021 (Secy)
Govt Rajaji Hospital, Madurai 625020.
Convenor
grhethicssecy @gmail.com.

Sub: Establishment-Govt. Rajaji Hospital, aMadurai-20-
Ethics committee-Meeting Agenda-communicated-regarding.

The Ethics Committee meeting of the Govt. Rajaji Hospital, Madurai was held at 11.00 Am to 1.00Pm on 28.06.2012 at the Dean Chamber, Govt. Rajaji Hospital, Madurai. The following members of the committee have been attended the meeting.

---

1. Dr.N.Vijayasankaran,M.ch(Uro.) 094-430-58793 0452-2584397	Sr.Consultant Urologist Madurai Kidney Centre, Sivagangai Road,Madurai	Chairman
2. Dr.P.K. Muthu Kumarasamy, M.D., 9843050911	Professor & H.O.D of Medical, Oncology(Retired)	Member Secretary
3. Dr.T.Meena,MD 094-437-74875	Professor of Physiology, Madurai Medical College	Member
4. Dr. S. Thamilarasi, M.D (Pharmacol)	Professor of pharmacology	
5.Dr.Moses K.Daniel MD(Gen.Medicine) 098-421-56066	Professor of Medicine Madurai Medical College	Member
6.Dr.M.Gobinath,MS(Gen.Surgery)	Professor of Surgery Madurai Medical College	Member
7.Dr.S. Dilshadh, MD(O&G) 9894053516	Professor of OP&Gyn Madurai Medical College	Member
8.Dr.S.Vadivel Murugan., M.D, 097-871-50040	Professor of Medicine Madurai Medical College	Member
9.Shri.M.Sridher,B.sc.B.L. 099-949-07400	Advocate, 2, Deputy collectors colony 4th street KK Nagar, Madurai-20.	Member
10.Shri.O.B.D.Bharat,B.sc., 094-437-14162	Businessman Plot No.588, K.K.Nagar,Madurai.20.	Member
11.Shri. S.sivakumar,M.A(Social) Mphil 093-444-84990	Sociologist, Plot No.51 F.F, K.K Nagar, Madurai.	Member

Following Projects were approved by the committee

Sl. No	Name of P.G.	Course	Name of the Project	Remarks
1.	Dr. Preethi Shahila. T	M.D Gen med	Salbutamol by metered-dose inhaler vs. nebulizer and spacer device for acute severe asthma.	Approved

Please note that the investigator should adhere the following: She/He should get a detailed informed consent from the patients/participants and maintain Confidentially.

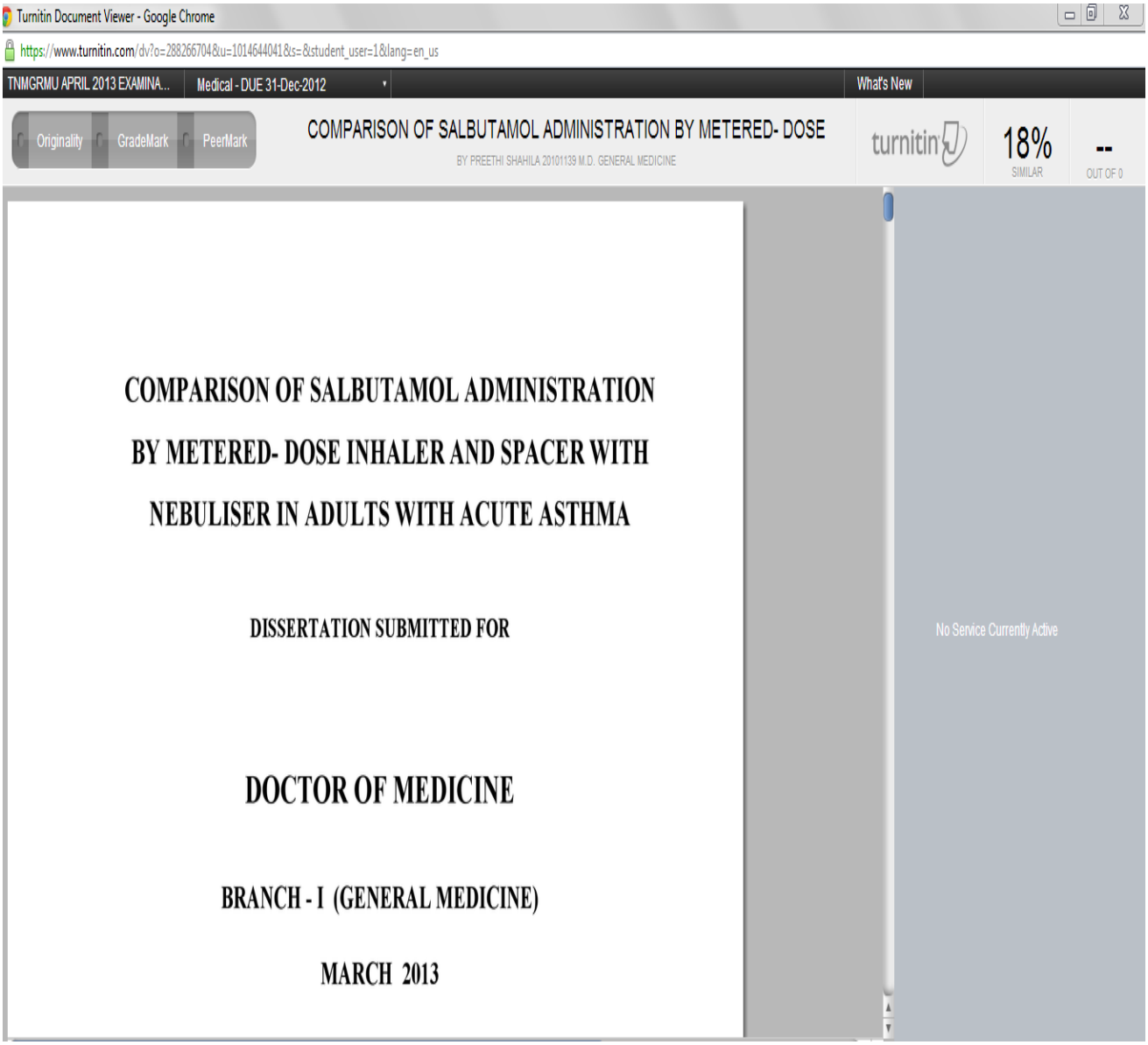
1. She/He should carry out the work without detrimental to regular activities as well as without extra expenditure to the institution to Government.
2. She/He should inform the institution Ethical Committee in case of any change of study procedure site and investigation or guide.
3. She/He should not deviate for the area of the work for which applied for Ethical clearance.
She/He should inform the IEC immediately, in case of any adverse events pr Serious adverse reactions.
4. She/he should abide to the rules and regulations of the institution.
5. She/He should complete the work within the specific period and apply for if any Extension of time is required She should apply for permission again and do the work.
6. She/He should submit the summary of the work to the Ethical Committee on Completion of the work.
7. She/He should not claim any funds from the institution while doing the word or on completion.
8.She/He should understand that the members of IEC have the right to monitor the work with prior intimation.

13.8.12

DEAN I/c

50/58

To
All the above members and Head of the Departments concerned.
All the Applicants.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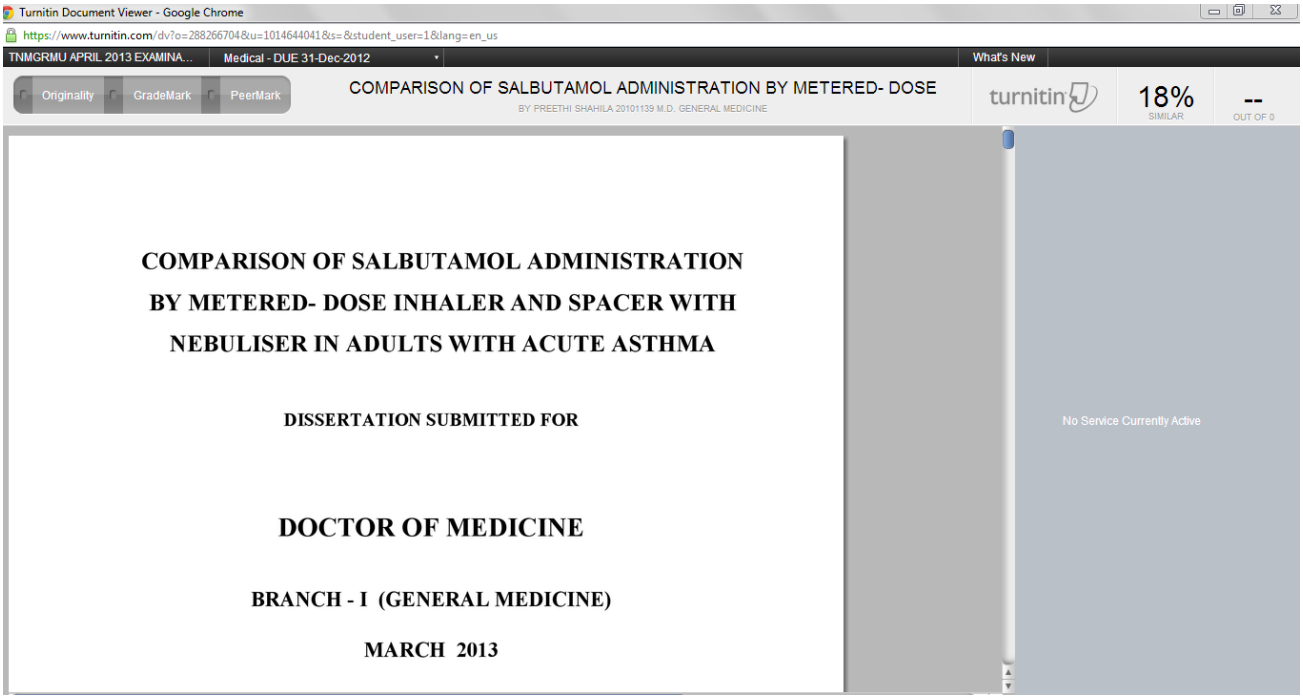
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